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HEALTH ASSESSMENT DOCUMENT
FOR
NICKEL AND NICKEL COMPOUNDS

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
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16. ABSTRACT

The predominant atmospheric forms of nickel are as sulfate, oxides, and complex oxides. Nickel also occurs in ambient and drinking waters and soils.

Routes of intake for man are inhalation, ingestion, and percutaneous absorption. Pulmonary absorption varies according to chemical and physical form of the compound. While gastrointestinal intake ranges from 300 to 500 μg daily, absorption is only one to ten percent of intake. Percutaneous absorption, usually through contact with nickel alloys in the household, is related to hypersensitivity and skin disorders. Inhaled nickel compounds lead to highest levels in lung, brain, kidney, and liver.

Nickel exposure produces chronic dermatological, respiratory, endocrine and cardiovascular effects. Reproductive and developmental effects have been found in animals but not humans. Various nickel compounds have been tested for mutagenicity, demonstrating the ability of nickel compounds to produce genotoxic effects; the translation of these effects into actual mutations is still not clearly understood. There is evidence both in humans and animals for the carcinogenicity of nickel in some forms. Lifetime cancer risks for continuous inhalation exposure at 1 μg nickel/m^3 have been estimated for nickel refinery dust and nickel subsulfide.

There is growing evidence that nickel may be an essential element for humans.

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PREFACE

The Office of Health and Environmental Assessment, in consultation with other Agency and non-Agency scientists, has prepared this health assessment to serve as a "source document" for Agency-wide use. Specifically, this document was prepared at the request of the Office of Air Quality Planning and Standards.

In the development of this assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared such that the toxicity of nickel and nickel compounds is qualitatively and, where possible, quantitatively identified. Observed effect levels and dose-response relationships are discussed where appropriate in order to place adverse health responses in perspective with observed environmental levels.

ABSTRACT

Nickel is found in nature as a component of silicate, sulfide, or, occasionally arsenide ores. It is a valuable mineral commodity because of its resistance to corrosion. Uses for nickel and its compounds include nickel alloys, electroplating baths, batteries, textile dyes and mordants, and catalysts. The predominant forms of nickel in the atmosphere are nickel sulfate, nickel oxides and complex oxides of nickel. Nickel is also found in ambient and drinking waters and soils as a result of both natural and anthropogenic sources.

Routes of nickel intake for man and animals are inhalation, ingestion, and percutaneous absorption. The pulmonary absorption of nickel compounds varies according to chemical and physical form, with insoluble compounds generally being cleared more slowly. Gastrointestinal intake of nickel by man is relatively high ranging from 300 to 500 µg daily; however, absorption is low, averaging one to ten percent of intake. Percutaneous absorption of nickel often occurs through contact with nickel-containing commodities used in food preparation; such contact is related to hypersensitivity and skin disorders. Absorbed nickel is carried by the blood and distributed to various tissues depending on route of intake. Inhaled nickel compounds lead to highest levels in lung, kidney, and liver, and, in the case of nickel carbonyl, high levels are also found in the brain. In humans, age-dependent accumulation appears to occur only in the lung. Unabsorbed dietary nickel is lost in the feces; urinary excretion is the major clearance route for absorbed nickel.

Nickel exposure produces chronic dermatological, respiratory, endocrine, and cardiovascular effects. Reproductive and developmental effects have been noted in animals but not in humans. Various nickel compounds have been tested for mutagenicity. In aggregate, these tests have demonstrated the ability of nickel compounds to produce genotoxic effects; however, the translation of these effects into actual mutations is still not clearly understood. There is evidence both in humans and animals for the carcinogenicity of nickel, at least in some forms. Lifetime cancer risks for continuous inhalation exposure at 1 µg nickel/m^3 have been estimated for nickel refinery dust and nickel subsulfide.

Although not conclusively established, there is growing evidence that nickel may be an essential element for humans.

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1. INTRODUCTION

In September, 1983, the Environmental Protection Agency's Office of Health and Environmental Assessment (OHEA) presented an external review draft of the Health Assessment Document for Nickel to the general public and to the Science Advisory Board (SAB) of the U.S. Environmental Protection Agency. Information within this draft document was presented in regard to total nickel exposures. At a public meeting in which this document was reviewed, the SAB and general public advised the Agency, where possible, to assess health risks associated with exposure to specific nickel compounds, rather than total nickel.

In response to this advice, the Agency undertook to revise the Health Assessment Document for Nickel to provide analyses of individual nickel compounds based upon existing information. The revised document is organized into chapters which include an executive summary of the information contained within the text of later chapters (Chapter 2); background information on the chemical and environmental aspects of nickel, including levels of various nickel compounds in media with which the U.S. population comes into contact (Chapter 3); information on nickel metabolism, where factors of absorption, tissue distribution, and excretion are discussed with reference to the toxicity of specific nickel compounds (Chapter 4); information on nickel toxicity, where acute, subacute, and chronic health effects of various nickel compounds in man and animals are discussed (Chapter 5); information on developmental and reproductive effects due to exposure to nickel compounds (Chapter 6); nickel mutagenesis information, where the ability of nickel compounds to cause mutations and other genotoxic effects are presented (Chapter 7); information on carcinogenesis, including dose-effect and dose-response relationships (chapter 8); and information on nickel as an essential element (Chapter 9).

This report is not intended to be an exhaustive review of all the nickel literature, but is focused upon those data thought to be most useful and relevant for human health risk assessment purposes. Literature was collected and reviewed up to April, 1985. Particular emphasis is placed on the delineation of health effects and risks associated with exposure to airborne nickel compounds. The primary purpose of this document is to serve as a basis for decision-making regarding the regulation of nickel and nickel compounds as hazardous air pollutants under pertinent sections of the Clean Air Act, as amended in 1977. Health effects associated with the ingestion of nickel or with exposure via other routes are also discussed, providing a basis for possible use for multimedia risk assessment purposes as well. The background information provided at the outset on sources, emissions, and ambient concentrations of nickel compounds in various media is presented in order to provide a general perspective against which to view the health effects evaluations contained in later chapters of the document.

The Agency recognizes that the regulatory decision-making process is a continuous one. The present document represents the state-of-the-knowledge as currently exists. To further this knowledge, the Agency has initiated a research project to study the health effects associated with exposure to specific nickel compounds as determined from reanalysis of epidemiologic studies. This project, headed by Sir Richard Doll of Oxford University, is a collaborative effort on the part of various epidemiologists, engineers, hygienists, and medical and data processing experts. Other sponsors of the research project include the Ontario Ministry of Labour; National Health and Welfare, Canada; Energy, Mines and Resources, Canada; the Nickel Producers Environmental Research Association; and the Commission of European Communities. The results of this research project will hopefully help to clarify the exposures of individual workers to specific nickel compounds and will yield greater insight into the association of such exposures with human health effects. Results of the project are expected to be available by mid-1988. As this and other new information that would warrant a re-evaluation of the present report becomes available, the Agency will undertake to evaluate this information as part of its mandate to protect the health of the general population.

2. SUMMARY AND CONCLUSIONS

2.1 BACKGROUND INFORMATION

2.1.1 Chemical/Physical Properties of Nickel and Nickel Compounds

Nickel is found in nature as a component of silicate, sulfide, or, occasionally, arsenide ores. It is a valuable mineral commodity because of its resistance to corrosion and its siderophilic nature which facilitates the formation of nickel-iron alloys. Stainless steel is the most well-known alloy; others include permanent magnet and super alloys, used in radios, generators and turbochargers, and copper-nickel alloys, used when resistance to extreme stress and temperature is required. Other uses for nickel and its compounds include electroplating baths, batteries, textile dyes and mordants, and catalysts.

As a member of the transition metal series, nickel is uniquely resistant to alkalis, but generally dissolves in dilute oxidizing acids. Nickel may exist in many oxidation states, the most prevalent being Ni^{2+}. Of some commercial and/or environmental significance are several binary nickel compounds including nickel oxide (both black, which is chemically reactive, and green, which is inert and refractory) and complex oxides of nickel, nickel sulfate, nickel nitrate, nickel carbonate, nickel hydroxide, nickel sulfide, and nickel carbonyl.

2.1.2 Nickel in the Ambient Air

In the atmosphere, nickel is present as a constituent of suspended particulate matter. The primary stationary source categories that emit nickel into ambient air are: primary production sources (nickel ore mining/smelting and nickel matte refining); combustion and incineration sources (coal and oil burning units in utility, industrial, commercial and residential use sectors, and municipal and sewage sludge incinerators); high temperature metallurgical sources (steel manufacturing, nickel alloy manufacturing, secondary nickel smelting, secondary nonferrous metals smelting, and iron and steel foundries); chemical and catalyst sources (nickel chemical manufacturing, electroplating, nickel-cadmium battery manufacturing and catalyst production, use and reclamation); and miscellaneous sources (co-product nickel recovery, cement manufacturing, coke ovens, asbestos mining/milling and cooling towers).

While nickel in its elemental state can be measured in the ambient air, determination of specific compounds is difficult to achieve. Techniques used to break down inorganic compounds into their ionic or atomic states change the form of the compound in the attempt to determine the total concentration of the element. In addition, the very low level of nickel present in ambient air samples (average of 0.008 $\mu g/m^3$; 1982 figures) complicates the situation. Nevertheless, by analyzing the physical and chemical properties of nickel, the forms of nickel input to various source processes, and the reaction conditions encountered in various source categories, it is possible to estimate forms of nickel emitted into the ambient air. From such analyses, the predominant forms appear to be nickel sulfate, complex oxides of nickel and other metals (chiefly iron), nickel oxide, and to a much lesser extent, metallic nickel and nickel subsulfide. Of the total volume of nickel emitted into the ambient air, the greatest contribution is from the combustion of fossil fuels in which nickel appears to be in the form of nickel sulfate, followed by lesser amounts of nickel oxide and complex metal oxides containing nickel.

2.1.3 Nickel in Ambient and Drinking Water

Nickel is usually found as Ni^{2+} in aquatic systems. Chemical factors which can affect the form of nickel in aquatic systems include pH and the presence of organic and inorganic ligands. Nickel is found in ambient waters as a result of chemical and physical degradation of rocks and soils, deposition of atmospheric nickel-containing particulate matter, and direct (and indirect) discharges from industrial processes. Of the anthropogenic sources of nickel in water, primary nickel production, metallurgical processes, fossil fuel combustion and incineration, and chemical and catalyst production are predominant.

Measurements of nickel in aqueous environments are generally reported as total nickel. The mean concentration of nickel in U.S. surface waters (based upon 1982 figures) ranges from less than 5 µg/l in the Great Basin of southern Nevada to greater than 600 µg/l in the Ohio River Basin. Concentrations in groundwater are also highly variable with means ranging from 4430 µg/l in the Ohio River basin to 2.95 µg/l in the Upper Mississippi River basin (based upon

1982 figures). A mean nickel concentration of 4.8 µg/l has been calculated for drinking water from eight metropolitan areas (based upon 1970 figures).

Specific forms of nickel in ambient waters have not been reported; however, inferences of species expected to be found in effluents can be made based on the nature of source processes and the aqueous chemistry of nickel. Nickel species in wastewaters from the major anthropogenic sources are likely to include dissolved salts (such as sulfates, chlorides and phosphates), insoluble oxides of nickel and other metals, and metallic nickel powder.

2.1.4 Nickel in Soil and Sediment

Many of the same chemical and physical properties which govern the behavior of nickel in aqueous environments also affect the behavior of nickel in soils and sediments. In soils, nickel may exist in several forms such as inorganic crystalline minerals or precipitates, as free ion or chelated metal complexes in soil solution, and as complexed with, or adsorbed to, inorganic cation exchange surfaces such as clays.

Naturally occurring nickel in soils depends upon the elemental composition of rocks in the upper crust of the earth. The natural concentration of nickel in soils usually ranges from 5 to 500 ppm, with an average level estimated at 50 ppm. Soils derived from serpentine rock (naturally high in nickel content) may contain nickel levels up to 5000 ppm. Anthropogenic sources of nickel to soils include emissions from primary smelters and metal refineries, disposal of sewage sludge or application of sludge as a fertilizer, auto emissions, and emissions from electric power utilities; the most significant of these sources being smelting and refining operations and sludge applications. Depending upon the source, nickel soil concentrations have been reported to range from 0.90 ppm (from auto emissions) to as much as 24,000 ppm (near metal refineries) to 53,000 ppm (from dried sludge). These figures are based upon elemental nickel as specific forms of nickel in soils have not been reported.

2.1.5 Nickel in Plants and Food

The primary route for nickel accumulation in plants is through root uptake from soil. Nickel is present in vegetation usually below the 1 ppm level, although plants grown in serpentine soils have been shown to have nickel concentrations as high as 100 ppm. For crops grown in soils where sewage sludge has been applied, nickel concentrations have been reported to range from 0.3 to 1150 ppm.

In addition to nickel uptake via soils, food processing methods have been shown to add to nickel levels already present in foodstuffs via leaching from nickel-containing alloys in food-processing equipment, the milling of flour, and the catalytic hydrogenation of fats and oils by use of nickel catalysts. The nickel content of various classes of food has been reported to range from 0.02 ppm (wet weight) in food items such as fresh tomatoes, frozen swordfish and pork chops to 9.80 ppm in cocoa.

2.1.6 The Global Cycling of Nickel

Nickel in all environmental compartments is continuously transferred between compartments by natural chemical and physical processes such as weathering, erosion, runoff, precipitation, stream/river flow and leaching. Nickel introduced into the environment by anthropogenic means is subject to the same chemical and physical processes, but can account for increased ambient concentrations in all environmental compartments. The ultimate sink for nickel is the ocean; however, the cycle is continuous because some nickel will leave the ocean as sea spray aerosols which burst and release minute nickel-containing particles into the atmosphere.

2.2 NICKEL METABOLISM

2.2.1 Absorption

Routes of nickel intake for man and animals are inhalation, ingestion and percutaneous absorption. Parenteral exposure of experimental animals is mainly of importance in assessing the kinetics of nickel transport, distribution and excretion. Parenteral exposure of humans to nickel from medications, hemodialysis and protheses can be a significant problem to certain sections of the population.

The relative amount of inhaled nickel which is absorbed from various compartments of the pulmonary tract is a function of both chemical and physical forms. Insoluble particulate nickel deposited in the various respiratory compartments in both occupationally exposed subjects and the general population is very slowly absorbed with accumulation over time. Experimental animal data show very slow clearance of deposited insoluble nickel oxide from the respiratory tract, moderate clearance (around 3 days) of the carbonate and rapid clearance (hours to several days) of soluble nickel salts. In the case of nickel oxide, clearance from lung involves both direct absorption into the blood stream and clearance via the lymphatic system. While most respiratory absorption studies demonstrate that differences in compound solubilities relate to pulmonary clearance, with inert compounds having relatively slower clearance, the relationship of respiratory absorption to pathogenic effects is still not clearly understood.

Gastrointestinal intake of nickel by man is relatively high compared to other toxic elements and can be partially accounted for by contributions of nickel from utensils and equipment in processing and home preparation of food. Average human dietary values range from 300 to 500 μg daily with absorption on the order of one to ten percent. Recent studies show that nickel bioavailability in human diets appears to be dependent on dietary composition.

Percutaneous absorption of nickel occurs and is related to nickel-induced hypersensitivity and skin disorders; however, the extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time. Transplacental transfer of nickel has been evidenced in rats and mice and several reports indicate that such passage can also occur in man.

2.2.2 Transport and Distribution

The kinetic processes governing the transport and distribution of nickel in various organisms are dependent upon the modes of absorption, the rate and level of nickel exposure, the chemical form of nickel and the physiological status of the organism. Absorbed nickel is carried by the blood, and although the extent of partitioning between erythrocytes and plasma or serum cannot be precisely stated, serum levels can be useful indicators of blood burden and, to a more limited extent, exposure status (excluding exposure to insoluble and unabsorbed nickel deposited in lungs). In unexposed individuals, serum nickel values are approximately 0.2 to 0.3 μg/dl. Albumin is the main macromolecular carrier of nickel in a number of species, including man, while in man and rabbit there also appear to be nickel-specific proteins.

Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in lung, brain, kidney, liver, and adrenals. Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver, and lung. Nickel absorption and tissue distribution following oral exposure appear to be dependent upon the relative amounts of the agent employed. Animal studies suggest that a homeostatic mechanism exists to regulate low levels of nickel intake (around 5 ppm), but that such regulation is overwhelmed in the face of large levels of nickel challenge.

Based on animal studies, nickel appears to have a very short half-time in the body of several days with little evidence for tissue accumulation. Human studies have shown that age-dependent accumulation of nickel appears to occur only in the case of the lung with other soft and mineralizing tissues showing no accumulation. There are very few data concerning nickel tissue levels and total body burden in humans. One estimate is that the total nickel burden in man is about 10 mg.

2.2.3 Excretion

The excretory routes for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake. Unabsorbed dietary nickel is lost in the feces. Urinary excretion in man and animals is usually the major clearance route for absorbed nickel, with biliary excretion also occurring in experimental animals. Sweat can also constitute a major route of nickel excretion. Recent studies suggest that normal levels of nickel in urine vary from 2 to 4 μg/l.

While hair deposition of nickel also appears to be an excretory mechanism, the relative magnitude of this route, compared to urinary excretion, is not fully known at present.

2.2.4 Factors Affecting Nickel Metabolism

A number of disease states or other physiological stresses can influence nickel metabolism in man. In particular, heart and renal disease, burn trauma, and heat exposure can either raise or lower serum nickel levels. To what extent factors such as age or nutritional status affect nickel metabolism in man is presently unknown. In animals, both antagonistic and synergistic relationships have been demonstrated for both nutritional factors and other toxicants.

2.3 NICKEL TOXICOLOGY

2.3.1 Subcellular and Cellular Aspects of Nickel Toxicity

Nickel, as the divalent ion, is known to bind to a variety of biomolecular species, such as nucleic acids and proteins, as well as their constituent units. Strongest interactions occur with sulfhydral, aza- and amino groups with binding to peptide (amido) and carboxylate ligands also possible.

A number of reports in the literature describe various *in vivo* and *in vitro* effects of various nickel compounds on enzyme systems as well as nucleic acid and protein biosynthesis. In particular, effects are seen on drug-detoxifying enzymes in various tissues, enzymes that mediate carbohydrate metabolism and enzymes that mediate transmembrane transport, such as ATPase.

A number of ultrastructural alterations are seen in cellular organelles from experimental animals exposed to various nickel compounds. Most of these changes involve the nucleus and mitochondria and range from slight changes in conformation to evidence of degeneration.

The behavior of cells in culture exposed to nickel compounds has been reported from different laboratories. Nickel ion, at varying levels, affects both viability and phagocytic activity of alveolar macrophages, which may explain the role of nickel in retarding resistance to respiratory tract infections in animal models.

Nickel-induced human lymphocyte transformation has been studied as a sensitive *in vitro* screening technique for nickel hypersensitivity and this procedure appears to be a reliable alternative to classical patch testing.

Various studies have been directed to the response of cells in culture to insoluble nickel dusts which are implicated in human and experimental animal carcinogenesis. In particular, rat embryo myoblasts show drastic reduction of mitotic index and viability when exposed to nickel subsulfide.

2.3.2 Acute Effects of Nickel Exposure

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl, $Ni(CO)_4$, exposure to which has been through accidental release to nickel-processing workers. Acute nickel carbonyl poisoning is clinically manifested by both immediate and delayed symptomology. With the onset of the delayed, insidious symptomology there are constrictive chest pain, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Most of these symptoms strongly resemble those of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in both man and animals. The pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage, edema, and cellular derangement. Patients surviving an acute episode of exposure may be left with pulmonary fibroses.

2.3.3 Chronic Effects of Nickel Exposure

2.3.3.1 Dermatological Effects of Nickel. Nickel dermatitis and other dermatological effects of nickel have been documented in both nickel worker populations and populations at large. Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological reports suggest that nonoccupational exposures to nickel-containing commodities may present significant problems to the general populace. Nonoccupational exposure to nickel includes nickel-containing jewelry, coins, tools, cooking utensils, stainless steel kitchens, prostheses, and clothing fasteners.

Clinically, nickel dermatitis is usually manifested as a papular or papulovesicular dermatitis with a tendency toward lichenification, having the characteristics of atopic rather than eczematous dermatitis. The hand eczema associated with nickel allergy appears to be of the pompholyx type, i.e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers.

A role for oral nickel in dermatitic responses by sensitive subjects has recently been described. Nickel-limited diets in one clinical trial resulted in marked improvement of hand eczema in half of the subjects while in a second study, nickel added to the diets of patients appeared to aggravate the allergic response. Further study of oral nickel-nickel sensitivity relationships should be conducted.

Nickel-containing implanted prostheses may provoke flare-ups of nickel dermatitis in nickel-sensitive individuals. The extent of this problem appears to depend on the relative ease with which nickel can be solubilized from the surface of the devices by action of extracellular fluid.

The underlying mechanisms of nickel sensitivity presumably include diffusion of nickel through the skin and subsequent binding of nickel ion.

Useful animal experimental models of nickel sensitivity are few and have been conducted only under very specialized conditions.

2.3.3.2 Respiratory Effects of Nickel. Noncarcinogenic effects of nickel in the human respiratory tract mainly derive from studies of nickel workers in certain production or use categories who have been exposed to various forms of nickel. In the aggregate, assessment of available human and animal data show two areas of possible concern for humans: (1) direct respiratory effects such as asthma, nasal septal perforations, and chronic rhinitis and sinusitis; and (2) increased risk for chronic respiratory tract infections secondary to the effect of nickel on the respiratory immune system.

2.3.3.3 Endocrine Effects of Nickel. A number of effects of nickel on endocrine-mediated physiological processes have been observed. In carbohydrate metabolism, nickel induces a rapid transitory hyperglycemia in rats, rabbits, and domestic fowl after parental exposure to nickel (II) salts. These changes may be associated with effects on alpha and beta cells in the pancreatic islets of Langerhans. Nickel also appears to affect the hypothalamic tract in animals, decreasing the release of prolactin. Decreased iodine uptake by the thyroid has also been observed when nickel chloride is inhaled or ingested. Human endocrine responses to nickel have been poorly studied, although hyperglycemia has been reported in workmen accidentally exposed to nickel carbonyl.

2.3.3.4 Cardiovascular Effects of Nickel. Experimental and clinical observations suggest that exogenous nickel II ion, and possibly endogenous nickel II, has a marked vasoconstrictive action on coronary vessels. Recent studies show that such action may be operative in patients with ischemic myocardial injury and in burn patients. Whether excessive nickel exposure in occupational or nonoccupational populations could exacerbate ischemic heart disease or enhance the risk of myocardial infarction in subjects with coronary artery disease is unknown but merits further study.

2.3.3.5 Reproductive and Developmental Effects of Nickel. Exposure to nickel has been shown to cause both reproductive and developmental effects in experimental animals; however, such effects have not been noted in man.

Specific reproductive effects seen in male rats include degenerative changes in the testis, epididymis and spermatozoa. Limited studies in female rats and hamsters suggest an effect on embryo viability and the implantation process. Such effects have been noted in animals exposed to excess amounts of nickel. In contrast, it has been demonstrated that a deficiency of dietary nickel can also lead to reproductive effects in the form of reduced litter sizes and decreased viability of newborn.

With respect to developmental toxicity, nickel exposure of animals prior to implantation has been associated with delayed embryonic development and possibly with increased resorptions. Structural malformations have been noted in avian species exposed to nickel salts. While similar malformations have also been seen in mammals, the data have been lacking in sufficient detail making determinations about significance difficult. Teratogenic effects of nickel carbonyl in mammals have been demonstrated in two rodent species.

2.3.3.6 Mutagenic Effects of Nickel. Various inorganic compounds of nickel have been tested for mutagenicity and other genotoxic effects in a variety of test systems. From these tests it appears that nickel may induce gene mutations in bacteria and cultured mammalian cells; however, the evidence is fairly weak. In addition, nickel appears to induce chromosomal aberrations in cultured mammalian cells and sister chromatid exchange in both cultured mammalian cells and human lymphocytes. However, the induction of chromosomal aberrations *in vivo* has not been observed. More definitive studies are needed to determine whether or not nickel is clastogenic. Nickel does appear to have the ability to induce morphological cell transformations *in vitro* and to interact with DNA resulting in crosslinks and strand breaks. In aggregate, studies have demonstrated the ability of nickel compounds to induce genotoxic effects; however, the translation of these effects into actual mutations is still not clearly understood.

2.3.3.7 Carcinogenic Effects of Nickel. There is evidence both in humans and animals for the carcinogenicity of nickel, at least in some forms. The human evidence of a cancer risk is strongest via inhalation in the sulfide nickel matte refining industry. This evidence includes a consistency of findings across many different studies in several different countries, specificity of tumor site (lung and nose), high relative risks, particularly for nasal cancer, and a dose-response relationship by length of exposure. There are also animal and *in vitro* studies on nickel compounds which support the concern that nickel, at least in some forms, should be considered carcinogenic. The animal studies have employed mainly injection as the route of exposure with some studies using inhalation as the exposure route. While the majority of the compounds tested in the injection studies have caused tumors at the injection site only, nickel acetate, when tested in strain A mice, and nickel carbonyl, at toxic levels, have also caused distal site primary tumors. The relevance of injection site only tumors in animals to human carcinogenic hazard via inhalation, ingestion, or cutaneous exposure is uncertain. Orally, in animals, three low-dose drinking water studies and one diet study with soluble nickel compounds have not shown any increase in tumors. Thus, nickel at least in some forms, should be considered carcinogenic to humans via inhalation, while the evidence via ingestion is inadequate.

Based on analysis of all the available data there are only three compounds or mixtures of nickel compounds that can currently be classified as either Group A (known human carcinogens) or B (probable human carcinogens), according to the Environmental Protection Agency's classification scheme for evaluating carcinogens (U.S. Environmental Protection Agency, 1984). Nickel refinery dust from pyrometallurgical sulfide nickel matte refineries is classified as Group A. The fact that nickel subsulfide is a major nickel component of this refinery dust, along with the evidence from animal and in vitro studies, is sufficient to conclude that nickel subsulfide is also in Group A. While there is inadequate evidence from epidemiologic studies with regard to evaluating the carcinogenicity of nickel carbonyl, there is sufficient evidence from animal studies to classify it as Group B2. The carcinogenic potential of other nickel compounds remains an important area for further investigation. Some biochemical and in vitro toxicological studies seem to indicate the nickel ion as a potential carcinogenic form of nickel and nickel compounds. If this is true, all nickel compounds might be potentially carcinogenic with potency differences related to their ability to enter and make the carcinogenic form of nickel available to a susceptible cell. However, at the present time, neither the bioavailability nor the carcinogenesis mechanism of nickel compounds is well understood.

Quantitatively, several data sets from nickel refinery workers provide sufficient exposure-response information both for testing model fits and for estimating incremental unit cancer risk. While the data partially support the use of both the additive and multiplicative excess risk models, neither is entirely satisfactory. Using both models and four data sets, a range of incremental unit risks from 1.1×10^{-5} $(\mu g/m^3)^{-1}$ to 4.6×10^{-4} $(\mu g/m^3)^{-1}$ has been calculated. Taking the midpoint of this range, the quantitative incremental unit risk estimate for nickel refinery dust is 2.4×10^{-4} $(\mu g/m^3)^{-1}$;

the quantitative unit risk estimate for nickel subsulfide, the most carcinogenic nickel compound in animals is twice that for nickel refinery dust. Comparing the potency of nickel subsulfide to 55 other compounds which the Environmental Protection Agency has evaluated as suspect or known human carcinogens, nickel subsulfide would rank between the second and third quartiles.

2.3.3.8 Other Toxic Effects of Nickel. Except for acute fatal exposures to nickel carbonyl, nickel compounds appear to possess low general neurotoxic potential. Lesions observed in neural tissue by nickel carbonyl include diffuse punctate hemorrhages, neural fiber degeneration, and marked edema.

Nickel subsulfide, when administered intrarenally to rats, provokes a pronounced, dose-dependent erythrocytosis associated with erythroid hyperplasia in bone marrow.

The effects of nickel chloride on the cellular and humoral immune responses of mice have been studied. Of particular note is the ability of nickel chloride to suppress the activity of natural killer cells within 24 hours of a single intramuscular injection. Such cells are thought to be one of the first lines of nonspecific defense against certain types of infection and tumors.

2.4 NICKEL AS AN ESSENTIAL ELEMENT

There is a growing body of literature which establishes an essential role for nickel, at least in experimental animals.

One key criterion for element essentiality--existence of specific nickel-deficiency syndromes--is reasonably satisfied for nickel. Various researchers have shown different systemic lesions in various animals deprived of dietary nickel. Nickel deprivation has an effect on body weight, reproductive capability, and viability of offspring and induces an anemia through reduced absorption of iron. Both antagonistic and synergistic interactions of nickel with various compounds have been noted to affect nutritional requirements.

Nickel also appears to be required in several proteins and enzymes. Jack bean urease (and possibly rumen microbial urease) has been shown to be such an enzyme. Recent studies on the activation of the calmodulin-dependent phosphoprotein phosphatase, calcineurin, suggests that nickel II may play a physiological role in the structural stability and full activation of this particular enzyme.

Further information in support of nickel as an essential element is the apparent existence of a homeostatic mechanism for regulating nickel metabolism and the existence of nickel proteins in man and rabbit. Although the evidence for the role of nickel in human physiology is not conclusively established, the transitory rise in circulatory nickel observed shortly after parturition has been linked to a possible role in control of atonic bleeding and placental separation.

2.5 POPULATIONS AT RISK

Among various subgroups of the U.S. population who may be at special risk for adverse effects of nickel are those who have nickel hypersensitivity and suffer chronic flare-ups of skin disorders with frank exposure. Within this category would be individuals predisposed to sensitization to nickel by virtue of familial history. In terms of the extent of nickel exposure among hypersensitive individuals, women who are housewives seem to be at particular risk. However, no data base exists by which to determine the prevalence of nickel hypersensitivity in the general U.S. population.

The extent to which nickel in inhaled cigarette smoke is a cofactor in the demonstrated association of smoking with various respiratory disorders is not defined at present, since various studies have presented conflicting information.

Nickel crosses the placental barrier in animals and apparently in man, thus exposing the conceptus to nickel. There is no information at present that nickel exposure _in utero_ under conditions of nickel exposure encountered by pregnant women in the U.S. population leads to adverse effects.

3. NICKEL BACKGROUND INFORMATION

3.1 PHYSICAL AND CHEMICAL PROPERTIES OF NICKEL AND NICKEL COMPOUNDS

Nickel is a silvery-white metal usually found in nature as a component of silicate, sulfide, or, occasionally, arsenide ores. Although the nickel content of some minerals is relatively high (up to 70 percent for heazlewoodite), nickel actually constitutes only about 0.008 percent of the earth's crust (National Academy of Sciences, 1975). The principal minerals associated with these ores are garnierite [$(Ni,Mg)_6Si_4O_{10}(OH)_8$], nickeliferous limonite [$(Fe,Ni)O(OH)\cdot NH_2O$] (Warner, 1984b), and pentlandite [$(FeNi)_9S_8$] (Duke, 1980). Native metallic nickel in a pure form is rarely observed. In the United States, nickel is mined as garnierite, a lateritic silicate ore, in which nickel is incorporated into the mineral's iron-magnesium lattice.

Nickel is a valuable mineral commodity because of its resistance to corrosion and its siderophilic nature which facilitates the formation of nickel-iron alloys. Stainless steel is perhaps the most well known alloy; others include permanent magnet and super alloys, which are used in radios, generators, and turbochargers. Copper-nickel and nickel-copper alloys, such as MONEL^{R}*, are used when resistance to corrosion is required. Nickel and its compounds are also used in electroplating baths, batteries, textile dyes and mordants, and catalysts.

3.1.1 Properties of Nickel and Nickel Compounds

3.1.1.1 Nickel. Elemental nickel, Ni, is a member of the Group VIII transition metal series and exhibits the properties presented in Table 3-1. Nickel is resistant to alkalis, but reacts with dilute acids (e.g., nitric acid), with the concommitant evolution of hydrogen. In certain situations, even oxidizing salts do not corrode nickel because the metal is made passive by formation of a surficial oxide film (Tien and Howson, 1980).

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* MONEL is a registered trademark of INCO, LIMITED.

TABLE 3-1. PHYSICAL PROPERTIES OF NICKEL AND NICKEL COMPOUNDS

Name	Formula	Formula Weight	Color, Crystalline Form	Density	Melting Point (°C)	Boiling Point (°C)	Solubility in 100 parts water
Nickel	Ni	58.71	silver, face-centered cubic	8.90	1455	2920	insoluble; soluble in dilute HNO_3
Nickel acetate tetrahydrate	$Ni(C_2H_3O_2)_2 \cdot 4H_2O$	248.86	green pyramidal	1.744	--	--	16; soluble in alcohol
Nickel ortho-arsenate	$Ni_3(AsO_4)_2$	453.97	yellow-green powder	4.982	--	--	insoluble
Nickel bromate hexahydrate	$Ni(BrO_3)_2 \cdot 6H_2O$	422.62	green monoclinic	2.60	--	--	28 (20°C)
Nickel bromide trihydrate	$NiBr_2 \cdot 3H_2O$	272.57	yellow-green deliquescent needles	--	loses H_2O 200	--	very soluble
Nickel carbonate	$NiCO_3$	118.72	light green rhombic	--	--	--	0.009 (25°C)
Nickel carbonate hydroxide	$NiCO_3 \cdot 2Ni(OH)_2$	304.17	green cubic	2.6	--	--	insoluble
Nickel chloride	$NiCl_2$	129.62	yellow deliquescent	3.55	1030	sublimes at 970	60.8 (20°C)
Nickel chloride hexahydrate	$NiCl_2 \cdot 6H_2O$	237.70	green monoclinic	--	--	--	111 (20°C)
Nickel fluoride	NiF_2	96.71	yellow-green tetragonal	4.72	1450	1740	2.56 (20°C)
Nickel hydroxide (hydrate)	$Ni(OH)_2 \cdot H_2O$	110.74	green powder	--	decomposes 230	--	solubility 0.0013 (20°C)
Nickel nitrate hexahydrate	$Ni(NO_3)_2 \cdot 6H_2O$	290.81	green monoclinic deliquescent	2.05	56.7	136.7	150 (20°C)
Nickel oxide	NiO	74.71	green cubic	7.45	2090	--	insoluble; soluble in acid
Nickel phosphate octahydrate	$Ni_3(PO_4)_2 \cdot 8H_2O$	510.20	light green powder	--	decomposes 600	--	insoluble; soluble in acid
Nickel sulfate hexahydrate	$NiSO_4 \cdot 6H_2O$	262.86	α blue-green tetragonal β green monoclinic	2.07 --	53.3 (forms β) loses water at 280	-- --	40.1 (20°C) 44.1 (20°C)
Nickel subsulfide	Ni_3S_2	240.26	light yellow cubic	5.82	790	--	insoluble; soluble in HNO_3

Dash indicates data not available.

Source: Antonsen (1980) and Dean (1979).

3.1.1.2 Nickel Compounds and Complexes. Transition metals such as nickel have unfilled electron subshells. Therefore, nickel may exist in the -1, 0, +1, +2, +3, or +4 oxidation states (Antonsen, 1980). The most prevalent form, however, is nickel II. The lower oxidation states usually occur in situations not normally encountered in the ambient environment (Cotton and Wilkinson, 1980), and the higher oxidation states of nickel are associated with compounds which are strong oxidizing agents and are not stable in water (Nieboer, 1981). Several binary nickel compounds are commercially and environmentally significant; a brief description of the chemistry of several of these compounds is presented below. Physical and chemical properties of nickel compounds are summarized in Table 3-1.

Nickel oxide, NiO, is available in two forms, each with different properties which are dependent upon the method of preparation. Black nickel oxide is chemically reactive and forms simple nickel salts in the presence of acids. It is used mainly in chemical processes. Green nickel oxide is inert and refractory. It is used primarily in metallurgical operations. Complex oxides of nickel and other metals may be formed during certain high temperature processes. An example is ferrite, $NiFe_2O_4$, which could be produced during the melting of material containing nickel and iron (Warner, 1983).

Nickel sulfate, produced commercially in larger quantities than any other nickel compound, is usually found as the hexahydrate salt ($NiSO_4 \cdot 6H_2O$), which is prepared commercially by adding nickel powder to sulfuric acid (Antonsen, 1980). When heated, the salt loses water and, above 800°C, decomposes into nickel oxide and sulfur trioxide (Antonsen, 1980). The sulfate is extremely soluble in water and sparingly soluble in ethanol.

Nickel nitrate hexahydrate, $Ni(NO_3)_2 \cdot 6H_2O$, also decomposes at high temperatures, with the intermediate formation of nickel nitrate. This nickel salt has a relatively low boiling point, 137°C (279°F), and is water soluble. The nitrate may be prepared by reacting nickel metal and nitric acid, and is used in batteries and sulfur-sensitive catalysts (Antonsen, 1980).

Nickel carbonate, $NiCO_3$, is only slightly soluble in water, but is soluble in acids and ammonium salt solutions. Commercially, the basic salt, $2NiCO_3 \cdot 3Ni(OH)_2 \cdot 4H_2O$, is the most important form. Nickel carbonate has been used as a glass colorant, in catalysts, and in electroplating baths. It has also been used to prepare specialty nickel compounds (Antonsen, 1980).

Nickel hydroxide, $Ni(OH)_2$, is insoluble in water but reacts with acids and aqueous ammonia (Cotton and Wilkinson, 1980). When placed in aqueous ammonia, the hydroxide forms the complex hexaamminenickel (II) hydroxide, $[Ni(NH_3)_6](OH)_2$, which is soluble (Cotton and Wilkinson, 1980). The hydroxide decomposes into nickel oxide and water at temperatures greater than 230°C (446°F) (Antonsen, 1980).

Nickel forms hydrous and anhydrous halides such as nickel chloride hexahydrate, $NiCl_2 \cdot 6H_2O$, and nickel chloride, $NiCl_2$; all nickel halides are soluble in water (Cotton and Wilkinson, 1980). These compounds are prepared from nickel metal or salts and the corresponding acid (Antonsen, 1980).

Nickel sulfide, NiS, is insoluble in water and may form naturally in bottom sediments of rivers and lakes under reducing conditions (Richter and Theis, 1980). The sulfide may be prepared commercially by the addition of sulfide ions (from ammonium sulfide) to aqueous solutions of Ni^{2+} ions, forming a black precipitate. The sulfide is originally freely soluble in acids, but, when exposed to air, the compound oxidizes to the insoluble Ni(OH)S (Cotton and Wilkinson, 1980). Other sulfides, Ni_3S_4, Ni_7S_6, and Ni_3S_2, are also known. Nickel subsulfide, Ni_3S_2, is insoluble in water but soluble in nitric acid.

Nickel carbonyl, $Ni(CO)_4$, is a colorless volatile liquid formed by passing carbon monoxide over freshly formed metallic nickel in the presence of an oxidant. The vapor density of nickel carbonyl is about four times that of air (Antonsen, 1980), indicating that nickel carbonyl in ambient air would tend to settle and not disperse. The compound decomposes at high temperatures, depositing pure metallic nickel. In ambient air, nickel carbonyl is relatively unstable and has a half-life of about 100 seconds (Stedman and Hikade, 1980). The carbonyl is insoluble in water but is miscible with most organic solvents.

Nickel forms coordination complexes in aqueous solutions in which negative groups or neutral polar molecules are attached to the nickel ion or atom (Stoeppler, 1980). Usual coordination numbers of these complexes are 4, 5, and 6, indicating that 4, 5, or 6 electron pairs are attracted by the nickel cation to form the complex (Cotton and Wilkinson, 1980). The geometric configurations of nickel complexes are octahedral or tetrahedral. For example, $[Ni(NH_3)_6](ClO_4)_2$ exhibits octrahedral configuration; the $[NiCl_4]^{2-}$ ion is tetrahedral in structure. The rate of formation of nickel complexes is relatively slow compared to other divalent cations (Nieboer, 1981). The difference in the rate of complex formation in solution is due in part to the high energy of formation of the trigonal pyramidal intermediates from the original octahedral configuration. In aqueous solutions, the Ni^{2+} ion is surrounded by six water molecules forming octahedral $[Ni(H_2O)_6]^{2+}$; the loss of a water molecule has been determined to be the rate limiting step (Nieboer, 1981). Several neutral ligands, especially amines, can displace water molecules of the complex nickel ion.

3.1.2 Environmental Chemistry of Nickel

3.1.2.1 Air. In the atmosphere, nickel is present as a constituent of suspended particulate matter (Barrie, 1981). Photooxidation and volatilization are not important chemical processes for nickel present on particles in ambient air. The properties of the individual nickel compound(s) associated with particulate matter determine the behavior of the element. For example, nickel's affinity for sulfur may lead to the emission of nickel sulfate-containing particulates from combustion sources. In the absence of sulfur, oxides of nickel may form. Differences in the solubilities of nickel sulfate and nickel oxide will affect the mobility of nickel in other environmental compartments following removal of nickel-containing particles from the atmosphere. As mentioned previously, oxides of nickel and other metals may be formed during high temperature processes involving these metals.

3.1.2.2 Water. Nickel is usually found as nickel II species in aquatic systems (Cotton and Wilkinson, 1980). The pH of the water, the redox potential and temperature of the system, and the presence of organic and inorganic ligands govern the form of nickel expected to be present in a given water system. For example, in natural fresh waters at pH 5 to 9, the Ni^{2+} ion (or more likely $[Ni(H_2O_6)]^{2+}$) is the dominant form (Richter and Theis, 1980). The divalent ion is extremely stable in aqueous solutions and can migrate over long distances (Callahan et al., 1979). In this pH range, nickel will also exist adsorbed to particulates, especially oxides of manganese and iron. Nickel complexes may form at this pH with the likelihood of formation as follows: $OH^- > SO_4^{2-} > Cl^- > NH_3$ (Richter and Theis, 1980). However, in aerobic environments, at pH less than 9, these nickel compounds are sufficiently soluble to maintain aqueous Ni^{2+} concentrations greater than $10^{-6}M$ (Callahan et al., 1979). Above pH 9, the carbonate and/or hydroxide precipitates out of solution.

The hydrolysis reaction, $Ni^{2+} + 2H_2O \rightarrow Ni(OH)_2 + 2H^+$, occurs most often in basic or alkaline systems. The various hydroxides of nickel which may be present as a function of pH and nickel concentration are shown in Figure 3-1.

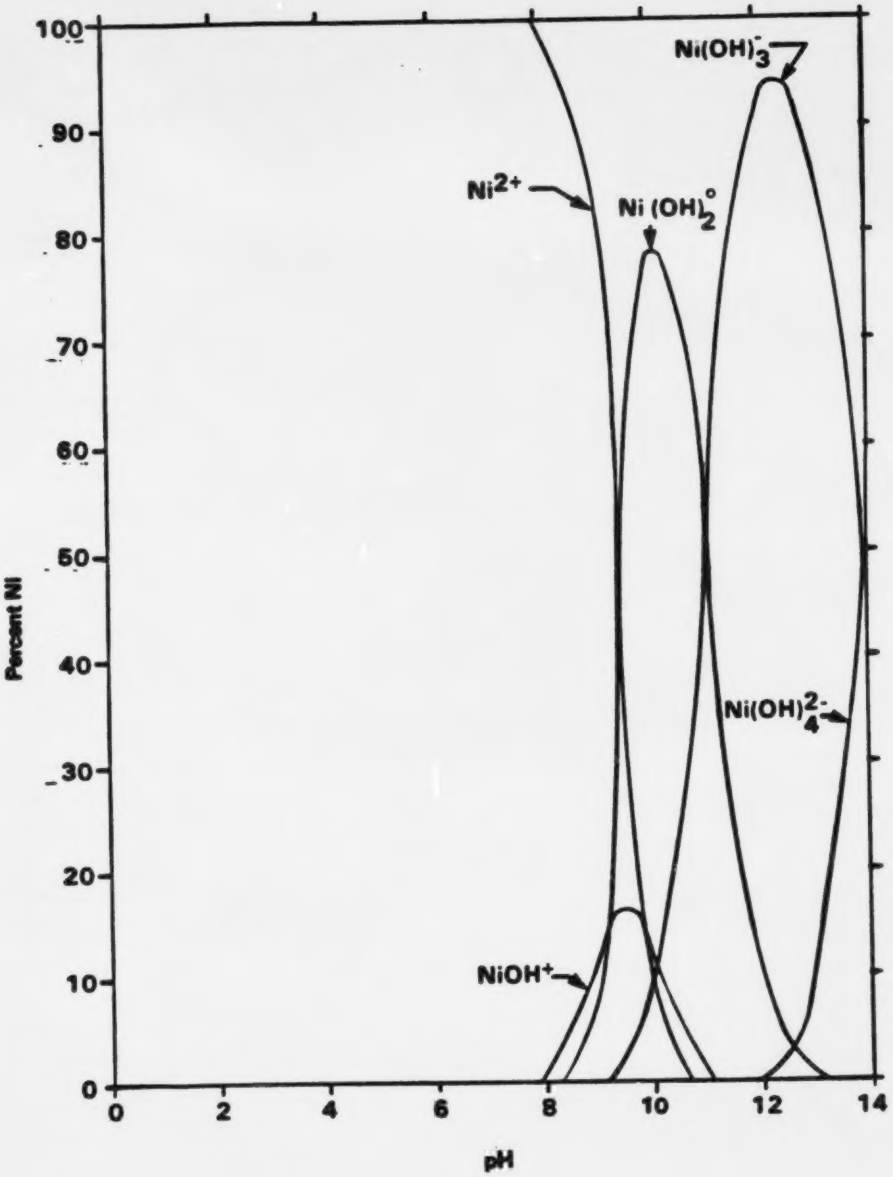

Figure 3-1. Nickel hydrolysis distribution diagram.
Source: Richter and Theis (1980)

Sulfate is a relatively weak nickel complex form (Richter and Theis, 1980), but at relatively high sulfate concentrations, nickel sulfate may be the dominant soluble form.

Based on a computer model, Sibley and Morgan (1975) report that in seawater, the predominant nickel species would be the dissolved ion. Little nickel would be predicted to be adsorbed to particulate matter because of the high ionic strength of seawater and the competition for binding sites by other cations such as Mg^{2+}, Ca^{2+}, and Na^+ (Sibley and Morgan, 1975).

3.1.2.3 Soil and Sediments. Many of the same chemical and physical properties which govern the behavior of nickel in aqueous environments also affect the behavior of nickel in soils and sediments. In soils, nickel may exist in several forms (Hutchinson et al., 1981) including:

- inorganic crystalline minerals or precipitates,
- complexed with or adsorbed to inorganic cation exchange surfaces such as clays,
- free ion or chelated metal complexes in soil solution (water soluble forms).

Nickel is held in the lattice structure of iron-magnesium minerals. The radius of the nickel ion, 69 picometers, may facilitate its substitution for magnesium (Mg^{2+}) (radius 65 picometers) or iron (Fe^{2+}) (radius 74 picometers) (Duke, 1980). As mentioned earlier, nickel compounds are often octahedrally coordinated. In rocks and minerals, it is usually so coordinated with oxygen as in the rock forming mineral olivine in which iron, magnesium, and nickel occur in octahedral sites (Duke, 1980). Such ferromagnesium minerals are fairly susceptible to weathering, and the nickel released is usually held in the weathered material in association with clay particles (Duke, 1980). Therefore, nickel is not considered to be very mobile in a soil surface environment.

In a soil/water system, nickel in the form of a divalent cation may form complexes with free organic or inorganic ligands present, including SO_4^{2-}, Cl^-, OH^-, CO_3^{2-}, humic/fulvic acids. Under anaerobic conditions and in the presence of sulfur, the insoluble sulfide, NiS, may form (National Academy of Sciences, 1975).

The pH is a dominant controlling factor in soil as well as water systems in determining adsorption, compound formation, and chemical precipitation. At pH greater than 9, the carbonate or hydroxide may precipitate. As the pH increases, nickel adsorption by iron and manganese oxides increases because of greater electrostatic attraction between the negative oxide surface and positive Ni^{2+} cation (Richter and Theis, 1980).

3.2 SAMPLING AND ANALYTICAL METHODS

3.2.1 Sampling for Nickel in Air

Trace amounts of nickel associated with atmospheric pollutants are almost always detected in the form of particulate matter. Accordingly, the sampling methods available for collecting air pollutants containing nickel are based upon principles of particulate measurement. Nickel may be measured in association with particulate matter in flue gas streams and in the ambient air. Nickel compounds may also be present in flue gas streams in vaporized forms. The principal methods for collecting nickel in emission streams are EPA Method 5, EPA Source Assessment Sampling System (SASS), or modifications of these two procedures. Nickel in the ambient air may be collected by high volume, dichotomous, cascade, and cyclone samplers.

The EPA reference method for sampling particulate emissions from stationary sources is EPA Method 5 as modified (F.R. 1977 August 18). This sampling method is excellent to use for nickel associated with particulate emissions from flue gas streams. It is not, however, designed to collect volatile inorganic components efficiently. Details on the sampling equipment and procedures of the method are given in the F.R. 1977 August 18 reference.

A method similar to EPA Method 5 has been developed by Peters (Peters et al., 1980) to sample inorganic compound emissions from stationary sources. The impinger system of the Peters method is appropriate for nickel sampling and can be easily modified if special trapping solutions are to be used for organometallic components from fuel combustion. A sample is collected from the system by combining the particulate matter collected on the filter with the impinger catches and the probe washes (acetone and nitric acid).

Several methods are available for collecting nickel that exists in a flue gas stream in both solid and gaseous phases. The EPA SASS has been a frequently used method for measuring nickel compounds from stationary sources. This method enables the collection of large quantities of particulate matter, classified according to size, and also enables the collection of volatile species that can be absorbed in liquid. A sample is recovered as in the EPA Method 5 train except that the solvent used for the probe wash is a 1:1 mixture of methylene chloride and methanol for the front half of the train and methylene chloride alone for the impinger system (Lentzen et al., 1978; Duke et al., 1977).

A flue gas sampling system designed to measure high pressure outputs under isokinetic conditions has been developed by Hamersma. The sampling method is used for emission streams at temperatures up to 500°C (932°F) and pressures greater than 300 psig. The detection limit is 60 $\mu g/m^3$ of the volatile trace element (e.g., nickel) in the gas stream (Hamersma and Reynolds, 1975).

A system for measuring trace inorganic compounds from normal pressure streams has been developed by Flegal (Flegal et al., 1975). The system is a modification of the EPA SASS methodology. The sampling method is used for emission streams at temperatures up to 270°C (518°F) and sampling rates up to 0.08 m^3 (3 ft^3)/min (Flegal et al., 1975).

The National Air Surveillance Network (National Academy of Sciences) has used a high-volume filtration sampler to collect nickel compounds in the ambient air (C.F.R., 1977). This method is used only for the measurement of particulate matter and is not capable of detecting unstable compounds such as nickel carbonyl.

3.2.2 Analytical Procedures for Nickel in Air

The determination of nickel, as the element, can be satisfactorily accomplished through various methods. However, a more specific determination of nickel to identify the types of nickel compounds present is difficult to achieve, particularly for ambient air samples. The identification of individual nickel compounds is complicated because techniques used to break down inorganic compounds into their ionic or atomic states change the form of the compound in the attempt to determine the total concentration of the element. Thus, the actual form and concentration of the nickel species present in the sample may not be accurately represented by the modified compound. The very low level of nickel present in ambient air samples (average of 0.008 $\mu g/m^3$ in 1982, see Table 3-2) complicates this identification.

Atomic absorption spectrophotometry with flame (AAF) is the most commonly used analytical procedure for measuring nickel in air samples. The detection limit for nickel by AAF has been identified as 0.05 μg/ml (Sachdev and West, 1970; Pickett and Koirtyohann, 1969). The linear range for accurate measurement

TABLE 3-2. CUMULATIVE FREQUENCY DISTRIBUTION OF INDIVIDUAL 24-HOUR AMBIENT AIR NICKEL LEVELS

Year	Network[a]	Sampler Type[b]	Number of Sites	Number of Observations	Percentile[c] 30	50	70	99	Arithmetic Mean	(SD)
1977	NASN	HiVol	238	5400	0.006	0.006	0.009	0.062	0.012	(0.019)
1978	NASN	HiVol	195	4147	0.003	0.006	0.010	0.067	0.010	(0.022)
1979	NASN	HiVol	160	2931	0.003	0.005	0.010	0.057	0.009	(0.012)
	IP	HiVol	65	602	0.006	0.015	0.023	0.128	0.021	(0.022)
	IP	SSI	15	211	0.011	0.017	0.026	0.135	0.024	(0.023)
	IP	Dicot T	49	364	0.010	0.012	0.019	0.078	0.019	(0.018)
	IP	Dicot C	49	364	0.005	0.005	0.006	0.026	0.007	(0.006)
	IP	Dicot F	49	364	0.005	0.006	0.012	0.053	0.012	(0.012)
1980	NAMFS	HiVol	142	2881	0.002	0.003	0.007	0.052	0.007	(0.013)
	IP	HiVol	132	1731	0.002	0.004	0.009	0.062	0.009	(0.014)
	IP	SSI	105	1302	0.001	0.003	0.007	0.058	0.008	(0.013)
	IP	Dicot T	72	759	0.010	0.010	0.012	0.057	0.015	(0.012)
	IP	Dicot C	72	759	0.005	0.005	0.005	0.020	0.006	(0.003)
	IP	Dicot F	72	759	0.005	0.005	0.006	0.040	0.009	(0.010)
1981	NAMFS	HiVol	160	3438	0.002	0.003	0.007	0.023	0.008	(0.007)
	IP	HiVol	150	1338	0.002	0.003	0.005	0.018	0.007	(0.005)
	IP	SSI	131	1039	0.002	0.003	0.005	0.015	0.007	(0.005)
	IP	Dicot T	119	847	0.047	0.098	0.255	1.83	0.056	(0.024)
	IP	Dicot C	119	847	0.031	0.067	0.196	1.63	0.047	(0.084)
	IP	Dicot F	119	847	0.010	0.018	0.036	0.274	0.009	(0.095)
1982	NAMFS	HiVol	119	2864	0.002	0.004	0.006	0.030	0.008	(0.009)
	IP	HiVol	90	645	0.002	0.004	0.005	0.014	0.007	(0.004)
	IP	Dicot T	128	872	0.010	0.010	0.011	0.025	NC[d]	NC
	IP	Dicot C	128	872	0.001	0.001	0.001	0.004	NC	NC
	IP	Dicot F	128	872	0.001	0.002	0.002	0.014	NC	NC
	IP	Dicot T*	19	34	0.013	0.013	0.013	0.014	0.007	NC
	IP	Dicot C*	19	34	0.001	0.001	0.001	0.001	NC	NC
	IP	Dicot F*	19	34	0.004	0.004	0.004	0.005	NC	NC

[a] Network: NASN is the National Air Surveillance Network which in 1980 was changed to the National Air Monitoring Filter Sites. IP is the Inhalable Particulate Network.

[b] Sampler Type: HiVol is the high volume air sampler which collects particles less than 50 μm diameter. SSI is the size selective (<15 μm) version of the HiVol. Dicot (T,C,F) is the dichotomous sampler where T is <15 μm, F is < 2.5 μm, and C is the difference, i.e., greater than 2.5 μm and <15 μm. Dicot (T*,C*,F*) is the dichotomous sampler, where T* <10 μm, F* <2.5 μm, and C* is the difference, i.e., greater than 2.5 μm and less than 10 μm.

[c] Values under given percentile indicate the percentage of stations below the given air level. Values in μg/m^3.

[d] Statistics not calculated if more than 50 percent of the values are below the lower limit of discrimination, approximately 0.001 μg/m^3.

Source: Evans (1984) and Akland (1981).

is reported as 0.2 to 0.5 μg/ml for a 232.0 nm wavelength setting. The known interferences for the analysis of nickel by AAF have been thought to be limited. However, there has been a reported case (National Institute for Occupational Safety and Health, 1977) where a hundredfold excess of iron, manganese, chromium, copper, cobalt, or zinc may decrease the absorbance recorded for nickel by as much as 12 percent. This situation may be avoided by the use of an oxidizing flame and the maintenance of proper burner elevation. In addition to the above case, a high concentration of organic solvents or solids in the aspirated solution will decrease absorbance at the 232.0 nm setting (National Institute of Occupational Safety and Health, 1977; National Academy of Sciences, 1975).

Atomic absorption spectrophotometry without flame is also a viable analytical technique for measuring nickel in ambient air samples. In this method, the nickel-containing sample is atomized directly in a graphite furnace, carbon rod, or tantalum filament instead of a flame. The nickel concentration is indicated by the absorption of a specific wavelength of light by the free atoms. For 100 μl of injected fluid, flameless AA has a detection limit for nickel of 0.1 μg/l (Perkin-Elmer, 1981).

X-ray fluorescence spectrometry (XRF) has been found to be a suitable technique for complex samples, such as fly ash, due to good reproducibility and rapid multi-element capabilities (Henry, 1979). The main advantages of this method are that the form of the sample is not critical for measurement and that the analytical procedure does not destroy the sample, thereby allowing reanalysis. The detection limit for XRF is 0.01 μg/cm^2 (Wagman et al., 1976). Inductively coupled argon plasma (ICAP) spectroscopy has gained prominence as a fast and reliable method for multi-element analysis involving inorganic compounds (F.R. 1979, December 3). The detection limit for this method is 15 μg/l at the 231.6 nm setting (U.S. Environmental Protection Agency, 1979). Nickel may also be determined colorimetrically with a complexation step. West and co-workers have adapted the ring-oven technique for the determination of nickel in particulate matter using dimethylglyoxime as the complexing agent (West, 1960). Spark source mass spectrometry (SSMS) has been used for comprehensive elemental analysis. The SSMS procedure is often used only to establish the presence of certain elements in a sample because this method is limited by low accuracies, usually on the order of 100 to 200 percent (Hamersma et al., 1979). However, sensitivities as low as 0.1 μg/g have been recorded (Henry, 1979). Neutron activation analysis (NAA) has also been used to determine nickel concentrations at the microgram level. However, the detection limit of NAA is only

0.7 µg/g. A final method for nickel determination is flame emission spectrophotometry (FES); this method is sensitive to 0.03 µg/ml of nickel in solution (Pickett and Koirtyohann, 1969).

Direct analysis techniques are being studied and used more extensively for determining specific inorganic compounds such as nickel species. These methods can provide for extremely accurate analysis and speciation of compounds because there is a low potential for compound alteration during analysis. However, problems inherent in this approach are that the compound must be analyzed in a crystalline matrix and that often only surface compounds are detected. X-ray diffraction (XRD) has been employed to determine the chemical structure of fossil fuel combustion fly ash. A lack of reference information complicates the identification process for compounds with unknown diffraction patterns (Henry, 1979). X-ray photoelectron spectroscopy (XPS) has been used to differentiate inorganic compounds that are in nitrogen and sulfur forms. Analysis for the potential application of this method for nickel speciation has not been done. A major limitation in regard to the potential application of this method to nickel analysis is that nickel can exist in both nitrogen and sulfur compounds, so differentiation of compounds may be difficult (Dod and Novakov, 1982). Secondary ion mass spectrometry (SIMS) has been used to determine the depth profile of a set of elements without regard to chemical form. A shortcoming of the method is that only surface compounds can be detected and thus, data interpretation is more difficult. Additional information about the chemical form of the element may be determined with the SIMS negative ion mode (Van Craen et al., 1982; Henry, 1979).

Fourier transform infrared spectroscopy (FT-IR) has also been employed for direct nickel measurement in coal and fly ash samples. The problems with this approach are: the specificity is not good, only surface compounds may be detected, and the applicability to trace nickel concentrations is questionable (Gendreau et al., 1980; Henry and Knapp, 1980; Henry, 1979). Information regarding compound form may be provided by several microscopy instrumental methods, including scanning electron microscopy (SEM), electron microprobe (EMP), scanning transmission electron microscopy (STEM), electron microscopy microanalyzer (EMMA), and ion microanalyzer (IMA). Compositional data on the elements present in the sample are provided by an energy dispersive X-ray analyzer (EDXA). These methods have been used alone or in combination to analyze coal combustion fly ash samples. The analytical responses are sensitive to interferences from background, particle mass, and interelement effects (Henry, 1979).

Inorganic compounds containing nickel in the vapor phase are readily speciated based upon the volatility of the compound. Brief described several different methods for the determination of nickel carbonyl (Brief et al., 1965). The range in sensitivity for these methods is from 0.008 to 0.10 μg/g.

The chemiluminescence method is faster and more specific than those methods described by Brief and can detect nickel carbonyl in air at parts per billion (by volume) levels (Stedman et al., 1979). In this method, nickel carbonyl is mixed with purified carbon monoxide and allowed to react with ozonized oxygen (O_2). The chemiluminescence generated by the reaction of these materials is measured as a signal of intensity. This intensity is proportional to the nickel carbonyl content of the sample. The nickel carbonyl content of the sample is determined by comparing the intensity of the sample signal to the intensity of a reference standard representing a known nickel carbonyl concentration.

3.2.3 Sampling for Nickel in Water

Nickel compounds in water are typically obtained by grab sampling. The type of grab sampling employed depends upon the form and consistency of the liquid sample. Three sampling methods are recommended: (1) tap sampling; (2) heat exchange sampling; and (3) dipper sampling. Tap sampling is commonly used for contained liquids in motion or static liquids in tanks or drums. This method may also be used for liquid slurries but there is an increased potential for unrepresentative sampling if the solids content exceeds ten percent. The sample is drawn through a clean Teflon line inserted into the sampling bottle. A valve is used to regulate the flow. Heat exchange sampling works in precisely the same manner as tap sampling except that it is employed for streams at temperatures $\geq$ 50°C (122°F) and therefore requires a condenser coil. The dipper sampling method is used for sampling sluices, ponds, or open discharge streams of thick slurry or stratified composition. The dipper sampling procedure is characterized by a flared bowl and an attached handle of sufficient height and breadth to reach a discharge area and provide for a cross-sectional sample (Hamersma et al., 1979).

The preservation of samples is accomplished by adding 0.1 N nitric acid to bring the sample solution to a pH of 2. This preservation step is necessary to avoid degradation of the sample during the collection, storage, and analysis period. Significant loss of trace elements during storage has been identified by several investigators (Owens et al., 1980; Struempler, 1973). A preconcentration step is often necessary for analytical methods to measure nickel, because it is usually measured in water at parts per billion levels (National Academy of Sciences, 1975). Sachdev and West (1970) recommend a concentration step using a mixed ligand. With preconcentration, there is also a potential for loss and contamination (Cassidy et al., 1982).

3.2.4 Analytical Procedures for Nickel in Water

Analysis of nickel in water is usually performed by atomic absorption spectrophotometry. The optimal concentration range for analysis is 0.3 to 5.0 mg/l using a wavelength of 232.0 nm. The sensitivity of this method, as reported by the U.S. Environmental Protection Agency (1979), is 0.15 mg/l and the detection limit is 0.05 mg/l. More recently, Greenberg and co-workers (1985) reported a detection limit of 0.02 μg/ml for nickel by flame AA and 0.001 μg/ml by graphite furnace AA.

Other analytical procedures for nickel in liquid samples are also employed. Multi-element techniques such as inductively coupled plasma emission spectrometry (ICPES) and spark source mass spectrometry (SSMS) are used when other elements besides nickel are being investigated. The ICPES method is used to give rapid and reasonably accurate determination of a specific group of 26 elements. The SSMS procedure is used to survey for the entire spectrum of elements. These procedures used for multi-element analysis are described in detail by Elgmork et al. (1973) and Johnson et al. (1972). Direct analysis for nickel in natural waters has been performed using high pressure liquid chromatography (HPLC). This procedure is capable of detecting nickel at pg/ml and ng/ml concentrations. A problem with this technique is the significant potential for interferences from organic components and colloids (Cassidy et al., 1982; Ugden and Bigley, 1977).

3.2.5 Sampling for Nickel in Soil

Sampling procedures for nickel compounds in soil may include any of the following methods: (a) trowel or scoop; (b) soil auger; or (c) Veihmeyer sampler. The optimal method for a particular situation depends upon the type of soil and the depth of soil profile required for analysis. The trowel or scoop is commonly used for dry surface soil. When the required soil profile is greater than three inches, a soil auger or Veihmeyer sampler should be used. The soil auger is not capable of collecting an undisturbed soil sample. The Veihmeyer sampler is difficult to use on rocky or wet soil (deVera et al., 1980).

Soil samples collected by any of the above procedures should be preserved for analysis in air-tight, high-density polyethylene containers. Large samples should be stored in metal containers lined with polyethylene bags (Duke et al., 1977).

3.2.6 Analytical Procedures for Nickel in Soil

Atomic absorption spectrophotometry is the most typically used method of analysis for nickel in soil (Theis and Padgett, 1983; Emmerich et al., 1982; Wiersma et al., 1979). The spark source mass spectrometry procedure is also frequently used (Hamersma et al., 1979; Lentzen et al., 1978). The sample must undergo acid extraction (acetic acid or nitric acid) before analysis. Several extraction test methods are available: (a) U.S. EPA extraction procedure; (b) ASTM Method A and Method B; and (c) IAEA (International Atomic Energy Agency) leach test (F.R. 1980, May 19; American Society for Testing and Materials, 1979; Hespe, 1971).

3.2.7 Sampling for Nickel in Biological Materials

The sampling methodology for nickel in biological materials requires the use of properly designed procedures to collect representative samples for analysis. The test must also adhere to approved guidelines involving precautionary measures to avoid contamination. Contamination can occur from the stainless steel apparatus used to collect biological samples or from containers used to store specimens (Stoeppler, 1980; Sunderman, 1980; Tolg, 1972). With certain biological samples such as urine, long-term storage is necessary for intercomparisons between samples. In such cases, the potential for loss due to adsorption on precipitates is significant and, thus, may result in an unrepresentative sample (Stoeppler, 1980).

3.2.8 Analytical Procedures for Nickel in Biological Materials

Routine analysis for nickel in biological materials is commonly performed by atomic absorption spectrophotometry. Anodic-stripping voltametry and isotope-dilution mass spectrometry are also used. Acid extraction is required before analysis of biological samples. Transfer of the sample into a form suitable for extraction requires wet- or dry-ashing (Stoeppler, 1980). The EPA Level 1 assessment procedures describe the Parr oxygen combustion technique for the preparation of all combustible materials for inorganic analysis (Lentzen et al., 1978). The prominent sources of error for these techniques are adsorption losses on the walls of the combustion chamber (dry-ashing) and additions through leaching from container walls (wet-ashing) (Stoeppler, 1980). A typical extraction procedure involves subjecting the samples to acid digestion and then separating the nickel from interfering elements by chloroform extraction of nickel dimethylglyoximate at alkaline pH. A similar extraction procedure involves ammonium pyrrolidine-methylisobutylketone (Horak and Sunderman, 1973; Nechay and Sunderman, 1973; Sunderman, 1973; Nomoto and Sunderman, 1970). Nickel is converted to the diethyldithiocarbamate complex and extracted into isomyl alcohol. The absorbance of nickel-bisdiethyldithiocarbamate is measured at 325 nm (Sunderman, 1971, 1967, 1965). Potential sources of error in the analysis of biological materials for nickel using acid extraction and atomic absorption spectrophotometry are: (a) contamination of the sample; (b) background absorbance; and (c) nonspecific absorbance caused by the presence of inorganic salts (Sunderman, 1984; Stoeppler, 1981, 1984; Nomoto and Sunderman, 1970). An International Union of Pure and Applied Chemistry (IUPAC) reference method for nickel in serum and urine using electrothermal atomic absorption spectrometry has been published (Brown et al., 1981).

3.3 SOURCES OF ATMOSPHERIC NICKEL

The discussion of nickel in ambient air is divided into two parts. The first part of the discussion concerns the determination of which species or forms of nickel are being emitted into ambient air by stationary sources. To augment the summarization in Section 3.3.1, a comprehensive and detailed treatment of nickel species in ambient air can be found in a recent report prepared for EPA's Office of Air Quality Planning and Standards by Radian Corporation (Brooks et al., 1984). In the second part of this section, available ambient air monitoring data for nickel are presented and characterized.

3.3.1 Nickel Species in Ambient Air

The primary stationary source categories which emit nickel into ambient air are coal and oil combustion, nickel ore mining/smelting, nickel matte refining, steel manufacturing, nickel alloy manufacturing, iron and steel foundries, secondary nickel smelting, smelting of other secondary nonferrous metals, co-product nickel recovery, refuse incineration, sewage sludge incineration, electroplating, nickel-cadmium battery manufacturing, nickel chemicals manufacturing, cooling towers, cement manufacturing, coke ovens, asbestos mining/milling, and nickel catalyst manufacture and reclamation. From these 19 individual source categories, five organizational groupings exist that generally describe the major species of nickel emitted into ambient air by anthropogenic sources. These groups include primary nickel production sources, combustion sources, high temperature metallurgical sources, chemical and catalyst sources, and other miscellaneous sources.

3.3.1.1 Primary Nickel Production. Primary nickel production sources include nickel ore mining/smelting and nickel matte refining. The only active nickel mine in the U.S. is located near Riddle, Oregon and is currently operated by the Hanna Mining Company. The Hanna Nickel Smelting Company, also located in Riddle, processes the mined nickel ore to produce a ferronickel containing 50 percent nickel and 50 percent iron. At the Hanna site, nickel air emissions are in the form of nickel silicate as this is the form of nickel within the mined mineral. Because the moisture content of the nickel ore is relatively high (about 20 percent), dust generation during mining is minimized and any emissions released tend to settle quickly in the vicinity of the source (Donaldson et al., 1978). Very few data are available to estimate the species of nickel emitted to air by the nickel ore smelting process. Ore crushing, drying, and calcining operations should be emitting nickel in the silicate mineral lattice because no chemical changes are occurring during these processes. Emissions from the high temperature ore roasting and melting furnaces used to produce ferronickel would contain nickel predominantly in the form of an oxide combined with iron as a ferrite or spinel (Warner, 1984a). Total nickel emissions from the nickel ore mining/smelting operation have been estimated to be approximately 8.4 Mg (9.3 tons)/yr (Doyle, 1984; Johnson, 1983; Oregon Department of Environmental Quality, 1981).

The AMAX Nickel Refining Company in Braithwaite, Louisiana is the only facility in the U.S. that refined imported nickel matte to produce nickel. This facility closed in late 1985. The discussion presented here describes emissions of nickel or nickel-containing substances associated with past practices at AMAX/Braithwaite.

Nickel emissions to ambient air from the AMAX refining operation were likely to have been in the forms of nickel subsulfide, metallic nickel, and to a much lesser extent, nickel oxide. Nickel subsulfide exists in particulate emissions associated with matte handling and preparation parts of the refining process because the processed mattes are sulfidic in nature (Page, 1983; Warner, 1983). XRD tests by the matte refining plant verified the existence of nickel subsulfide emissions (Gordy, 1984). Metallic nickel powder was generated by the matte refining plant as a final product and was emitted during drying, packaging, and briquetting operations. Nickel oxide could also have been emitted from the plant sintering operation as some metallic nickel was likely to have been oxidized in the high temperature sinter furnace (Warner, 1983). Total nickel emissions from the matte refining facility have been estimated to be approximately 6.7 Mg (7.4 tons)/yr (Kucera, 1983; Radian Corporation, 1983).

3.3.1.2 Combustion and Incineration. Combustion sources include coal and oil burning units in utility, industrial, commercial, and residential use sectors, and incineration sources such as municipal refuse and sewage sludge incinerators. Ambient air monitoring samples taken near coal and oil combustion sites have not been analyzed to speciate which forms of nickel they may contain. However, several studies have analyzed the fly ash which is emitted into the air from combustion sources for the purpose of speciating trace elements. In fly ash samples collected from the stacks of five oil-fired utility boilers, the nickel components were found to be 60 to 100 percent water soluble (Henry and Knapp, 1980). In the analysis of leachate from the solubility test, sulfate anion was the only anion present at more than trace levels. With this information, it can be postulated that the form of nickel in the fly ash emissions and ambient air from oil-fired combustion is predominantly nickel sulfate. This theory was eventually confirmed after the fly ash and the soluble and insoluble fractions were analyzed by Fourier transform infrared spectroscopy (Gendreau et al., 1980). In another study of stack fly ash and scale samples taken from the reducing and oxidizing sections of an oil-fired utility boiler, nickel was found to exist as nickel ammonium sulfate [$Ni(NH_4)_2(SO_4)_2 \cdot 6H_2O$] (Blaha et al., 1979).

In the insoluble fraction of the fly ash samples from oil-fired boilers, nickel was determined by XRD to potentially exist as nickel oxide (Henry and Knapp, 1980). However, with XRD patterns it is frequently difficult to distinguish between pure nickel oxide and complex metal oxides involving nickel. Potentially, the nickel component of the insoluble fraction could exist as nickel oxides, such as ferrites, aluminates, and vanadates; a combination of metal oxides, including nickel and nickel oxide; or purely nickel oxide as the XRD results suggest.

Tests on five oil-fired utility boilers by Dietz and Wieser (1983) produced results showing that water soluble metal components of emitted fly ash exist primarily as metal sulfates. The portion of the total amount of nickel present in the fly ash samples that was water soluble ranged from 15 (±4) to 93 (±4) percent, with the average being 54 (±9) percent. Because the ion chromatograph sulfate levels of the samples were on the average less than the expected sulfate levels based on stoichiometric considerations, Dietz and Wieser (1983) postulated that some small part of the soluble nickel may have been present as partially soluble oxides or very finely dispersed particles of metal oxides. The insoluble nickel components of the oil combustion fly ash were reported to be simple metal oxides. Dietz and Wieser (1983) reported nickel oxide to be present in the emissions. As no mention was specifically made of complex oxides containing nickel and other metals, it is uncertain whether the authors found such complexes.

In summary, it appears that particles found in ambient air as a result of oil combustion may contain nickel predominantly in the form of nickel sulfate, with lesser amounts as nickel oxide and complex metal oxides containing nickel.

Henry and Knapp (1980) performed solubility and component analysis studies for fly ash from coal combustion similar to those discussed above for oil combustion. Samples of fly ash emitted from coal-fired utility boilers were water leached, and the fraction of nickel found to be soluble ranged from 20 to 80 percent. As in the case of oil combustion, sulfate was the major anion present; therefore, in the soluble fraction of fly ash from coal combustion, nickel probably exists as nickel sulfate. Various metal sulfates were identified in the soluble fraction of the coal combustion fly ash by XRD and FT-IR, but specific compounds were not reported (Henry and Knapp, 1980). Hansen and Fisher (1980) and Hansen et al. (1984) conducted experiments on coal combustion fly ash particles which indicated that the majority of nickel present was soluble and that this soluble portion was associated primarily with sulfate anions, and to a much lesser extent, fluoride and phosphate anions. Eatough et al. (1981) confirmed the existence of Ni^{+2} associated with sulfate in the soluble portion of emissions from an oil-fired power plant.

The insoluble fractions of the coal combustion fly ash were determined by XRD to contain metal oxides, although neither nickel oxide nor complex oxides containing nickel were specifically identified. Hulett et al. (1980) suggested that nickel in the insoluble phase of coal combustion fly ash exists as a substituted spinel of the form $Fe_{3-x}Ni_xO_4$. Hansen et al. (1981) substantiated the results of Hulett et al. (1980) by demonstrating that the insoluble portion of coal combustion fly ash contains nickel as a component of complex metal (primarily iron) oxides.

The forms of nickel emitted to ambient air from coal combustion appear to be essentially the same as those from oil combustion, i.e., predominantly nickel sulfate with less as nickel oxide or oxides of nickel and other metals.

National atmospheric nickel emissions from coal and oil combustion dominate releases from all other nickel emission source categories. Recent studies have estimated nationwide nickel emissions from coal and oil combustion to be from 2,600 to 8,500 Mg (2,860 to 9,350 tons)/yr. Of the total amount of nickel emissions from coal and oil combustion, oil combustion has been estimated to account for 60 to 98 percent (Krishnan and Hellwig, 1982; Systems Applications Incorporated, 1982; Baig et al., 1981). The American Petroleum Institute (API), however, has recently estimated lower emissions of nickel from petroleum fuel combustion, ranging from 1,725 Mg to 2,400 Mg (1,900 to 2,640 tons/yr) (API, 1986).

The results of one recent study of a metropolitan area in California support the possibility that oil combustion contributes a significant amount of nickel to ambient air particles, particularly in the fine (less than 10 µm) size fraction (Cass and McRae, 1983). Routine air monitoring data from sites in the South Coast Air Basin were evaluated to reconcile the original source of particular trace elements found in the samples. Approximately 81 percent of the nickel found was determined to be present as fly ash from residual fuel oil combustion (Cass and McRae, 1983). In contrast, however, a similar study was performed on ambient air monitoring samples taken from the Washington, D.C. area, and nickel particles could not be associated with any particular source category, combustion, or otherwise (Kowalczyk et al., 1982).

Support for the theory that the majority of nickel in ambient air is water soluble and is in the form of nickel sulfate can be found in the work by Cawse (1974). Cawse (1974) measured the bulk deposition of many elements, including nickel, at seven nonurban ambient air monitoring sites in Great Britain. The soluble nickel component as a percentage of total nickel deposition ranged from

47 to 80 percent, with the average level being 59 percent. The major anion measured in these samples was sulfate, implying the possible existence and predominance of nickel in ambient air as nickel sulfate. The experiments of Spengler and Thurston (1983) would lead to the speculation that instead of nickel sulfate, nickel exists in ambient air to a large extent as nickel ammonium sulfate.

An absolute species characterization of potential nickel emissions from refuse and sludge incinerators is difficult because the compositions of waste streams vary so greatly between units and may vary daily within the same unit. Recent tests on the fly ash emissions of three refuse and three sludge incinerators have shown that one-third to one-half of the emissions are water soluble. The soluble phase of refuse incinerator emissions contained principally chloride and sulfate ions, thereby suggesting that nickel can be present in this phase as nickel chloride or sulfate (Henry et al., 1982). The insoluble portion of refuse incinerator emissions contained primarily oxide and silicate salts of various metals. Although not specifically identified, complex oxides of nickel and other metals (mainly iron) are probably the prevalent forms of nickel that would exist (Henry et al., 1982).

The water soluble phase of the sludge incinerator fly ash was found to contain predominantly sulfate ions, although chloride, nitrates, and phosphates were present at much lower levels. The fraction of total nickel that was water soluble in sludge incinerator fly ash ranged from 34 to 52 percent (Henry et al., 1982). It is reasonable to expect that nickel emissions present in the water soluble phase of sludge incinerator emissions are predominantly nickel sulfate, with potentially much lower amounts of nickel chloride, nitrate, and phosphate. The insoluble phase of sludge incinerator fly ash emissions was similar to that of refuse incinerator emissions, and the probability is great that nickel exists predominantly as complex oxides of nickel and other metals. It is highly likely that nickel was combined with iron to form a spinel; however, such a conclusion was not explicitly determined (Henry et al., 1982).

3.3.1.3 Metallurgical Processes. The nickel source categories included in the high temperature metallurgical grouping include steel manufacturing, nickel alloy manufacturing, secondary nickel smelting, other secondary nonferrous metals smelting, and iron and steel foundries. In the high temperature processes occurring in metallurgical furnaces, the majority of nickel in emissions would be expected to be oxidized. Data from the steelmaking industry and from the related nickel alloy industry confirm that the majority of nickel present in emissions from metallurgical melting furnaces is in the form of complex oxides of nickel and other metals (Page, 1983; Koponen et al., 1981). In one test of nickel emissions from an electric arc furnace (EAF) producing stainless steel, only five percent of the total nickel present was water soluble (Koponen et al., 1981). The nickel in the insoluble phase was determined to exist as an alloyed element in iron oxide particles. Tests of the emissions from an EAF producing carbon steel showed nickel oxide to constitute from zero to three percent of the total particulate emissions. Similar work on the emissions from a refining vessel handling specialty steel showed one sample where nickel oxide was reported to constitute 3.1 percent of total particulate emissions (Emission Standards and Engineering Division, 1983; Andolina, 1980). It was not clearly documented in these studies whether the emission samples contained pure nickel oxide or another oxide of nickel, possibly involving additional metals. The data suggest that instead of being pure nickel oxide, the reported values likely represented total nickel present, expressed in terms of calculated percentages of pure oxides (i.e., nickel oxide).

Several dust samples have been collected during the manufacture of different nickel alloys and analyzed using XRD, SEM, and EDXA (Page, 1983). X-ray diffraction patterns of the dusts closely matched the reference patterns for nickel oxide and a complex copper-nickel oxide. Dusts from the manufacture of another variety of nickel alloy were thought to contain nickel oxide and a complex iron-nickel oxide. The presence of metallic nickel in nickel alloy dusts emitted to the air has also been verified (Page, 1983).

The only sulfur compound of nickel expected to be emitted from high temperature metallurgical processes is nickel sulfate. If sulfur is present (usually as sulfur dioxide) in metallurgical processes, sulfate and consequently nickel sulfate may be formed rather than nickel sulfide or nickel subsulfide. Nickel sulfate would be formed because it is thermodynamically more stable under these types of temperature conditions than either of the sulfide compounds (Page, 1983). When such emissions are released into ambient air, any nickel sulfides would be unstable relative to nickel sulfate.

The available test results indicate that nickel in high temperature metallurgical environments is predominantly oxidized and combined with other metals present (if stoichiometry permits) to form complex oxides of nickel and other metals. Nationwide nickel emissions from steelmaking and nickel alloy manufacturing, the dominant emission categories of the metallurgical group, have been estimated to be 71 Mg (79 tons)/yr and 66 Mg (73 tons)/yr, respectively (Young, 1983; McNamara et al., 1981).

3.3.1.4 Nickel Chemicals and Catalysts. The nickel chemical and catalysts grouping includes nickel chemical manufacturing, nickel electroplating, nickel-cadmium battery manufacturing, and nickel catalyst production, use, and reclamation source categories. These source categories are grouped together because each uses various nickel compounds directly as process input materials and this chemically dictates the form of nickel air emissions. Emissions of nickel from the production of nickel chemicals are thought to be small (McNamara et al., 1981). Raw material handling and product drying, grinding, and packaging are the operations which most likely emit nickel. Nickel in raw material form will generally be metallic nickel or nickel oxide, while nickel as a product can exist as nickel sulfate (the highest volume nickel chemical produced) or any of 25 other nickel chemicals produced in the United States.

Nickel emissions can potentially occur from electroplating shops during the handling of nickel salts used to prepare plating baths, the plating of nickel, and grinding, polishing, and cutting operations performed on the finished product and scrap metal. Nickel emitted during preparation and from misting during plating are in the form of the chemical used, generally nickel sulfate or chloride. Emissions from grinding and polishing operations contain metallic nickel particles (Radian Corporation, 1983).

Nickel chemicals are used in nickel-cadmium battery manufacturing primarily for battery plate construction. The forms of nickel most likely to be emitted by a battery plant are metallic nickel, nickel oxide, nickel nitrate, and nickel hydroxide (Radian Corporation, 1983; Radakovich, 1978). No specific data are available to indicate which form nickel emissions may take during the production, use, and reclamation of nickel catalysts. During catalyst preparation, nickel can be emitted as fugitive dusts of the raw material such as nickel carbonate, hydroxide, nitrate, or acetate (McNamara et al., 1981). Nickel is used, in finely divided form, as a catalyst in the hydrogenation of oils; however, no data were found to indicate the magnitude of nickel emissions from this source. During the recycling of nickel catalysts, nickel may be emitted as an oxide since the metal is subjected to high temperatures required for thermal decomposition. Based on limited source testing data, nickel emissions from catalyst recycling appear to be minimal (Vellella, 1984).

3.3.1.5 Miscellaneous Nickel Sources. Other miscellaneous categories of nickel air emission sources include co-product nickel recovery, cement manufacturing, coke ovens, asbestos mining/milling, and cooling towers. Nickel can be emitted during cement manufacturing, asbestos mining/milling, and coking operations because nickel is a natural component of the minerals used in these processes. During cement manufacturing, nickel is emitted either as a component of the clays, limestones, and shales used as raw materials or as an oxide formed in the high temperature process kilns. Nickel emitted to air from asbestos mining/milling is in the form of the silicate minerals from which the majority of asbestos is obtained. No specific data are available on the species of nickel emitted from coke ovens; however, because the atmosphere of a coke oven is highly reducing, nickel emissions can be theorized to be in the forms of nickel sulfides (Ni_3S_2 and NiS) and nickel metal (Ni^0). When these nickel-containing particles are released into ambient air, oxidation takes place. The extent of this oxidation is governed by the temperature at which the particles pass from the reducing atmosphere into ambient air.

Nickel can be emitted from cooling towers because nickel salts are used in cooling tower water as biocides. The exact form of nickel emitted with tower drift depends on the chemical characteristics of the cooling water and the presence of ligands which can bind nickel ions (Richter and Theis, 1980). Potentially nickel could be released as hydroxides, sulfates, or chlorides, and as nickel ions.

Co-product nickel recovery means the recovery of nickel compounds during the electrolytic refinement of blister copper and platinum. Nickel sulfate is emitted during these processes from drying and packaging operations (McNamara et al., 1981).

3.3.2 Ambient Air Nickel Levels

The most comprehensive assessment of nickel levels in ambient air of the United States is currently performed by the U.S. Environmental Protection Agency. Nickel levels are assessed by EPA through its National Air Monitoring Filter Sites (NAMFS) network and its Inhalable Particulate (IP) network. The NAMFS system was known as the National Air Surveillance Network (NASN) prior to 1980.

In the NAMFS network, ambient air particulate samples are taken using high volume (HiVol) ambient air samplers and are analyzed for their nickel content by ICAP spectrometry. In the IP network both HiVol samples and dichotomous (dichot) filter samples are taken. Inhalable Particulate network HiVol samples are analyzed using ICAP spectrometry, while XRF spectroscopy is used on dichotomous filter samples. Further discussions of analytical procedures are found in Section 3.2.

Data from the NAMFS and IP networks have been compiled in Table 3-2 (see Section 3.2.2). Table 3-2 presents the cumulative frequency distribution of individual 24-hour ambient air nickel levels for the period 1977 to 1982. For the National Academy of Sciences (NAMFS) data there appears to be a general downward trend as the 1977 mean of 0.012 $\mu g/m^3$ fell to 0.008 $\mu g/m^3$ in 1982. In 1977, 99 percent of the National Academy of Sciences data points were less than 0.062 $\mu g/m^3$, but in 1982 the level at which the 99th percentile was gauged at being less than was only 0.030 $\mu g/m^3$. The IP network HiVol data show a similar downward trend. The mean IP HiVol value in 1979 was 0.021 $\mu g/m^3$ but was only 0.007 $\mu g/m^3$ in 1982. The 99th percentile value for the IP network HiVols had an even greater decrease than the National Academy of Sciences data, from 0.128 $\mu g/m^3$ to 0.014 $\mu g/m^3$.

The IP network dichot data also show a decreasing trend for nickel in ambient air with the exception of the elevated values in 1981. No information is available within the IP system to explain this perturbation. An examination of the raw nickel data for 1981 showed that the majority of the values were at or only slightly above the lower limit of discrimination (0.001 $\mu g/m^3$). There were only a few elevated readings; however, these few were elevated to such an extent that the averages in Table 3-2 resulted. Because the sampling and analysis took place on a year round basis, seasonal variations could not be listed as the cause for the higher values shown for IP dichots in 1981. In 1982, the IP network dichots reflect a significant decline in ambient nickel levels. Many of the data were below the lower limit of discrimination. Inhalable Particulate network dichot data for 1982 show a fairly distinct declining trend for ambient air nickel levels when compared with similar numbers for 1979 and 1980.

A large amount of urban and nonurban site specific ambient nickel data are available from the NAMFS network. These data, which are too expansive to present here, are a part of the National Aerometric Data Bank maintained by the

U.S. EPA at Research Triangle Park, North Carolina. They may be obtained from the Monitoring and Data Analysis Division of the Office of Air Quality Planning and Standards at Research Triangle Park, North Carolina.

3.4 NICKEL IN AMBIENT WATERS

Nickel is found in ambient waters as a result of chemical and physical degradation of rocks and soils, deposition of atmospheric nickel-containing particulate matter, and direct (and indirect) discharges from industrial processes. The concentration of nickel in U.S. surface waters recorded in the U.S. Environmental Protection Agency's Storage and Retrieval (STORET) data base ranges from less than 5 µg/l to greater than 1,000 µg/l (STORET, 1984). A mean nickel concentration of 4.8 µg/l was calculated for drinking water in the United States following a survey of 969 water supplies covering eight metropolitan areas (National Academy of Sciences, 1975). About 90 percent of the samples taken in this survey contained less than 10 µg/l.

The anthropogenic sources of nickel in waters are briefly discussed in this section. Attempts are made to determine the species or form of nickel expected to be found in the effluents based on the nature of the process and the aqueous chemistry of nickel. The concentrations of nickel in ambient water are also reviewed and characterized.

3.4.1 Nickel Species in Water

The major anthropogenic sources of nickel in water are associated with primary nickel production, other metallurgical processes, fossil fuel combustion and incineration, and the production and use of nickel chemicals and catalysts. Other industrial processes, such as cement manufacture, asbestos mining and milling, and coke production release less significant amounts of nickel to surface and groundwaters.

3.4.1.1 Primary Nickel Production. Domestic primary nickel production is limited to the production of ferronickel by the Hanna Mining Company and the Hanna Smelting Company in Riddle, Oregon. Refining of imported nickel-containing matte was performed by the AMAX Nickel Division in Braithwaite, Louisiana, until late 1985.

The chief sources of wastewater at Hanna include those associated with:

- conveyor belt washing
- scrubbers for ore dryers
- once-through cooling
- slag granulation
- ferronickel shot production

No data were found which identified the form or species of nickel in wastewater from Hanna. However, by examining the form of nickel associated with each wastewater source and applying some concepts of nickel behavior in aqueous media, some general hypotheses may be formed. Any nickel found in wastewaters associated with belt washing and scrubbers for ore dryers should be in the same form as in the ore (a silicate mineral) since these processes do not involve significant chemical changes in the ore. Nickel in wastewaters from slag granulation and ferronickel shot production may be found as an iron-nickel oxide, condensed and oxidized from molten ferronickel fumes.

At AMAX, potential aqueous discharges included spent electrolyte solution and tailings from pressure leaching vessels. Although no information was found which quantified the volume of effluent streams or their nickel content, discharges of nickel from the AMAX facility were probably small. Hoppe (1977) reported that greater than 99 percent of the nickel contained in initial feedstock (matte) was recovered.

Nickel in tailing pond discharges may have been present as the ion, Ni^{2+}, or the dissolved sulfate from electrolyte solutions. A small amount of the insoluble nickel subsulfide may have been present due to dusts from matte handling and storage. Likewise, small amounts of metallic nickel powder may have been contained in tailing ponds from floor washing and dust removal in the powder production area.

3.4.1.2 Metallurgical Processes. Approximately 75 percent of the nickel consumed in the U.S. is used to produce stainless steel, cast iron, and alloys (Sibley, 1983). In general, each of these metals is produced by melting nickel and other required materials, refining the molten metal, and pouring the melt into ingots or slabs. Hot working, cold working, and annealing are used to obtain the desired final product (coils, sheets, strips). No definitive data were found which identified the species of nickel discharged in effluents from these processes.

Based on analyses of a high alloy nickel plant by INCO (Page, 1983), nickel in wastewater associated with air pollution control equipment may be present for the most part as an oxide of nickel and other metals present in the alloy (iron, copper, chromium), as a soluble compound (perhaps the sulfate), or as metallic nickel. Although its presence was not substantiated by XRD, some nickel oxide may be contained in these effluents.

Nickel has also been detected in discharges from hot or cold working processes (mainly cooling water) and in pickling liquor. Contact cooling water may contain particulate matter dislodged from nickel-containing slabs or billets. Therefore, nickel could exist in these effluents as dissolved nickel or as nickel alloy particles. Pickling or scale removal uses hydrochloric or sulfuric acids to remove oxidized film (scale) accumulated on slags as they are hot-worked. Although nickel oxide is insoluble in water, it is soluble in acids; iron oxides are also acid soluble. Therefore, if the oxide film is nickel oxide or iron-nickel oxide, nickel discharged in pickling liquors could exist as dissolved nickel ion, or in an oxidized form.

3.4.1.3 Combustion and Incineration. Combustion of fossil fuels and incineration of municipal refuse and sewage sludge release nickel into all environmental media because the metal is contained in materials being burned. The actual combustion process does not generate aqueous effluents, but the subsystems required for boilers and incinerators such as ash disposal, cooling water, waste ponds, and certain types of air pollution control equipment generate significant volumes of wastewater with varying nickel contents.

No substantive data were found in the literature which identified the form of nickel contained in boiler or incinerator effluents. Based on analyses of atmospheric emissions, the control of which generates much of the wastewater, and the chemistry of nickel, some speculation as to the speciation of nickel in these effluents can be made. Based on analyses by Henry and Knapp (1980) and Hulett et al. (1980), nickel in fly ash from both utility and industrial combustion of fossil fuel could be present as the dissolved sulfate or a relatively insoluble oxide of nickel and other metals. These forms would also be found in ash disposal wastewater streams.

Boiler blowdown and metal cleaning streams contain products of corrosion, scale buildup, and various acids and alkalis (Baig et al., 1981). This effluent could contain nickel as the dissolved ion, especially if alkaline materials are used to neutralize the effluent, keeping the pH between 7 and 9. Overall nickel discharged in an effluent from fossil fuel combustion facilities would most likely be present as the soluble sulfate, a complex oxide of nickel and other metals (silicate, spinel, ferrite), and the nickel ion.

Wastewater sources from refuse incinerators include spray chamber water, used to remove fly ash, and bottom ash quench water. Nickel found in incinerator effluent may be present as it is in fly ash since most wastewater discharges are associated with ash disposal or removal. Henry et al. (1982) found that in refuse derived fly ash, the soluble portions were mostly sulfate and chloride salts; solubles from sludge fly ash included sulfate, chloride, and phosphate salts. The insoluble fractions were oxides, silicates, and in sludge ash, some insoluble phosphates. Therefore, in aqueous effluents associated with incinerator ash disposal, nickel may be found as the dissolved sulfate, chloride, or phosphate species. Some nickel may be found associated with silicates and oxides.

3.4.1.4 Nickel Chemicals and Catalysts. Nickel compounds are consumed for the most part in electroplating and the production of nickel-cadmium batteries. Because of the close relationship between the primary producers and consumers of nickel compounds, the species of nickel in aqueous effluents associated with these industry segments are reviewed together in this section. Discharges from catalyst manufacture and use are also included here.

Although a wide variety of nickel compounds are produced commercially in the U.S. (the halide salts, carbonate, hydroxide, acetate), nickel sulfate is the most important commercially. Aqueous discharges of nickel during sulfate production apparently are minimal. Effluent discharges are minimized by extensive recycling of both process solids and liquids. The species of nickel discharged would most likely be nickel sulfate, either dissolved or as the sulfate compound. Some unreacted metallic nickel powder or nickel oxide may be present in effluent, but extensive recycling and material conservation precludes the discharge of significant quantities of raw material.

Discharges of nickel from the production of other nickel compounds could contain dissolved nickel ion or the compound itself, depending on the solubility of the compound and the quality of the receiving waters.

As mentioned previously, several nickel chemicals are used to formulate electroplating baths. Although plant effluents are extensively recycled, some nickel may escape recovery during in-plant wastewater treatment. Depending on the concentration of the nickel salt in the bath, nickel is likely to be discharged as the Ni^{2+} ion or as the nickel salt (sulfate, chloride, etc.).

Nickel powder and nickel nitrate salts are the raw materials used to produce sintered plate nickel-cadmium batteries. Process wastewaters are generated by washing and rinsing battery plates. Based on the forms of nickel used in the process, including nickel nitrate, nickel hydroxide, and a nickel powder (assumed to be metallic nickel), it seems reasonable to project that these compounds would be present in wastewaters. Depending on the pH of the receiving waters and the presence of ligands, nickel discharged from battery manufacturing could exist as divalent Ni^{2+}, metallic nickel, or as the hydroxide. No data were found to conclusively substantiate these projections.

Nickel-containing catalysts are used in the hydrogenation of fats and oils, the hydrotreating of petroleum, and in various ammonolysis and methanation reactions. They are also used in the catalytic combustion of organic compounds in automobile exhausts. Wastewater sources were not definitively identified, but may include caustic leachate from Raney^{R} nickel production, filtrate from the manufacture of precipitated or supported catalysts, and water used in air pollution control equipment. The form of nickel present depends on the type of nickel in raw materials, which may be an aluminum-nickel alloy, nickel powder, or a solution of soluble salts such as chlorides, acetates, nitrates, or sulfates (Antonsen, 1980). Nickel in wastewaters may be the dissolved form of these compounds.

3.4.1.5 Other Sources of Aqueous Discharges of Nickel. Because nickel is contained in raw materials, the metal may be detected in effluents from processes such as the production of cement and coke, and from asbestos mining and milling. Nickel has also been detected in cooling tower discharge at concentrations greater than that of intake water. The species of nickel potentially emitted in effluents from these source categories are described below.

Cement Manufacture

Nickel is contained in raw materials such as limestone, gypsum, and shale, which are used in the production of Portland cement. The major wastewater stream associated with cement production is that from filtration or flotation of slurried feed materials to remove mica, quartz, and other impurities (Katari et al., 1974). Any nickel present would most likely be held in the mineral lattice of the parent raw material (limestone, sand, etc.).

Coke Ovens

By-product coke production requires thermal distillation of coal. Wastewater sources associated with this source category include quenching water, and water required for air pollution control equipment. Although no definitive data were found which identified the form of nickel in such effluent, it seems probable that nickel may be in an oxidized form because of the high temperatures of the coking process.

Asbestos Mining

No wastewater is generated during dry processing of asbestos minerals. At the single plant using wet processing, approximately 68 percent of the water is recirculated and 4 percent becomes incorporated into the final product (U.S. Environmental Protection Agency, 1976). Twenty percent is discharged to a settling pond; eight percent is lost in tailings disposal. Tailing pile runoff may contain nickel leached from the mineral, especially under acidic conditions. Nickel would be present as it occurs in the mineral, substituted in the magnesium-silicate structure. No data were found to indicate the magnitude of such discharges or to identify the form of nickel present.

Cooling Towers

Waslenchuk (1982) analyzed the intake and discharge waters of a power plant cooling system which relied on saline intake water, and reported that discharge waters contained 0.3 to 1.9 µg more dissolved nickel per kilogram than intake waters after a two-minute transit time through the system. The form of nickel in discharge waters and the persistence and fate of the metal in the receiving water body depend on the aqueous chemistry of the metal. Nickel could be removed from the water column by adsorption to sediments. In the Waslenchuk study, adsorption to sediments apparently exerted a significant influence on the fate of dissolved nickel. Therefore, nickel in cooling tower discharge may enter the receiving water body as a cation and, depending on the presence of ligands, suspended particulate, water pH and hardness, the ion may form complexes, be adsorbed, or precipitate out of solution.

3.4.2 Concentrations of Nickel in Ambient Waters

The concentrations of nickel in surface waters are generally low unless impacted directly or indirectly by industrial processes. The STORET data base (STORET, 1984) compiles sampling data for surface water, well water, and other parameters for the United States. The unremarked surface water data for the

15 major river basins in the continental U.S. were retrieved for 1980 to 1982. As shown in Table 3-3, mean total nickel concentrations for these river basins ranged from less than 5 µg/l to greater than 700 µg/l during the three-year period. Although differences in the number of samples taken per year limits the accuracy of speculating upward or downward trends in nickel concentration, it can be seen that the Ohio River basin consistently shows the highest mean nickel concentration, ranging from 552 µg/l in 1980 to 672 µg/l in 1982. The maximum reported concentrations for this basin were between 7,800 and 10,900 µg/l.

In 1980, 11 of the 15 basins had mean total nickel concentrations of less than 50 µg/l. During that year, highest mean concentrations were observed in the Ohio River, Northeast, Southeast, Western Gulf, and Tennessee River basins. The Great Basin (the southern Nevada area) had the lowest mean. For the 8,037 unremarked observations recorded in the STORET system that year, the mean for all basins was 68.2 µg nickel/l. Ten of the basins (66 percent) had concentrations such that 85 percent of the reported values were less than 100 µg/l.

For 1981, the Ohio River basin again showed the highest mean concentration, 742 µg/l; the South basin reported the second highest mean of 68.3 µg/l. The remaining 13 basins had mean nickel concentrations of less than 50 µg/l. In 1982, all areas except the Ohio River basin reported means of less than 50 µg/l.

Figure 3-2 shows the concentrations of nickel detected in surface waters of counties throughout the continental United States, documented by sampling in 1982. The gradations on the map are made as percentiles, meaning that 85 percent of the values reported fall into the ranges given on each map. The darkest shadings indicate that 85 percent of the samples in that county are greater than 26 µg/l in 1982. Although it is somewhat difficult to make comparisons between areas because of variations in the number of samples and sampling location, the map indicates that greater quantities of nickel are found in the Ohio-Pennsylvania area, some Rocky Mountain states (Utah, Wyoming, Colorado), and Oklahoma. Similar geographic patterns in regard to nickel concentrations have been found over the past several years prior to 1982.

Concentrations of nickel in groundwater, as shown in Table 3-4, are also highly variable. Fewer river basins are represented in this data base (as compared to surface water data), and fewer samples were taken during the same three-year period. From Table 3-4 it is apparent that groundwaters from the Ohio River basin show substantially higher nickel concentrations for all three

TABLE 3-3. NICKEL CONCENTRATIONS IN U.S. AMBIENT SURFACE WATERS: 1980 - 1982 (μg/l)

	1980				1981				1982			
Major River Basin	n	mean	max	85 percentile	n	mean	max	85 percentile	n	mean	max	85 percentile
Northeast	628	82.7	9,140	105.0	377	9.50	150	17.0	232	9.83	190	15.0
North Atlantic	518	26.4	920	40.0	687	35.0	560	50.0	455	37.8	1,210	50.0
Southeast	962	77.6	900	173.0	527	68.3	500	190.0	647	45.4	480	100.0
Tennessee River	56	56.2	780	100.0	94	48.6	3,450	20.0	232	15.0	965	20.0
Ohio River	1,921	552.0	10,900	700.0	1,019	742.0	9,000	100.0	882	672.0	7,800	180.0
Lake Erie	155	26.2	200	100.0	264	26.2	1,000	50.0	185	10.9	260	10.0
Upper Mississippi River	350	14.3	500	11.0	366	18.3	1,700	13.0	386	14.1	1,000	19.0
Lake Michigan	126	14.2	120	20.0	159	10.1	79	10.0	120	15.2	700	10.0
Missouri River	749	24.8	1,300	26.0	705	13.5	280	20.0	513	16.1	270	30.0
South Central Lower Mississippi River	831	31.9	1,110	46.0	634	20.4	660	27.0	487	15.3	300	25.0
Colorado River	362	19.4	300	30.0	429	19.8	570	25.0	295	28.1	910	26.0
Western Gulf	570	46.7	251	84.0	159	11.1	180	17.0	144	29.8	540	20.0
Pacific Northeast	783	18.5	480	20.0	261	23.1	470	30.0	155	18.8	280	30.0
California	94	26.6	200	54.0	246	45.0	575	88.0	352	44.8	538	70.0
Great Basin	32	4.81	12	11.0	33	3.21	11	5.0	17	3.94	10	6.0
TOTAL OBSERVATIONS	8,037				5,960				5,102			
MEAN (all basins)		68.2				72.9				65.1		

NOTE: Remarked data excluded. N = number of observations. 85 percentile means that 85 percent of all recorded values are less than the given value.

Source: STORET (1984).

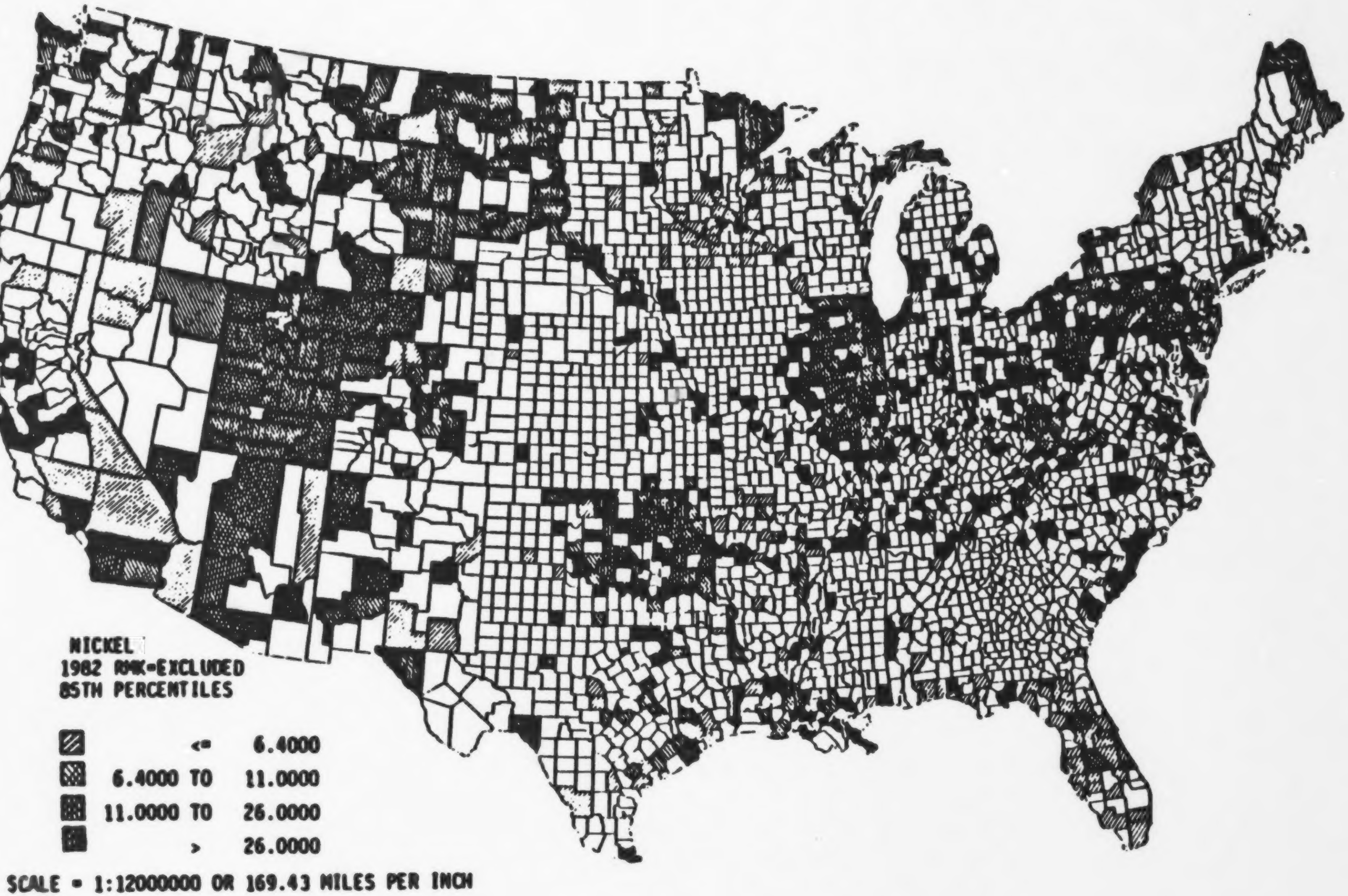
NICKEL
1982 RMK=EXCLUDED
85TH PERCENTILES
<= 6.4000
6.4000 TO 11.0000
11.0000 TO 26.0000
> 26.0000
SCALE = 1:12000000 OR 169.43 MILES PER INCH

Figure 3-2. Concentrations of nickel in surface waters, by county, 1982.

Source: STORET (1984).

TABLE 3-4. NICKEL CONCENTRATIONS IN GROUNDWATER: 1980 - 1982 (μg/l)

	1980				1981				1982			
Major River Basin	n	mean	max	85 percentile	n	mean	max	85 percentile	n	mean	max	85 percentile
North Atlantic	92	12.4	110	20.0	182	13.5	340	20.0	178	30.9	306	50.0
Southeast	123	85.1	2,500	130.0	323	754.0	44,000	300.0	218	129.0	17,800	180.0
Tennessee River					1	50.0	50	50.0	23	7.13	42	13.0
Ohio River	49	6,300	18,300	9,000	54	4,710	20,700	7,500	39	4,430	19,600	6,700.0
Upper Mississippi River	6	13.3	32	32.0	9	3.38	9	6.0	6	2.95	5.90	5.90
Western Gulf									5	18.0	24	24.0
Pacific Northwest	2	6.0	11	11.0								
California					2	99.0	180	180.0	1	100.0	100	100.0
TOTAL OBSERVATIONS	272				571				470			

NOTE: Remarked data excluded, blanks indicate data not available. N = number of observations. 85 percentile means that 85 percent of all recorded values are less than the given value.

Source: STORET (1984).

years for which data were retrieved. This trend is similar to that seen in surface waters. The Southeast basin reported the second highest concentrations, with means ranging from 85.1 to 754 µg/l. The California basin also has relatively high concentrations of nickel in groundwater, but these data were obtained from only three samples taken between 1981 and 1982. The remaining basins all had mean nickel concentrations in groundwater of less than 50 µg/l.

It must be noted that the extremely high concentrations found in the Ohio River and Southeast basins may not truly reflect the extent of nickel presence in groundwaters for each basin area because one or two samples may have skewed the data toward higher concentrations. This is verified somewhat by the data for the Southeast basin in 1980 where the maximum reported value was 2,500 µg/l but 85 percent of the remaining samples contained less than 130 µg/l.

3.5 NICKEL IN OTHER MEDIA

The presence of nickel species in other media such as soil, plants, and food constitutes a potential source of population exposure. Nickel may enter these media through deposition on soils with a subsequent release in a soluble form that is available to plants, including those used as food (National Academy of Sciences, 1975). Significant factors determining the extent of release to plants are: (a) the soil pH, decreases in which generally result in larger releases to plants; (b) the relative amount of soil cation exchange sites; and (c) the relative amounts of other cations in the soil (Hutchinson et al., 1981). The concentrations of nickel are examined in this section for three interrelated media: soils, plants, and food. The measured levels are reported as elemental nickel owing to the fact that speciation data on nickel are unavailable in the literature.

3.5.1 Nickel in Soils

The level of naturally occurring nickel in soils depends upon the elemental composition of rocks in the upper crust of the earth. These rocks provide most of the material from which soils derive their inorganic constituents. The crust of the earth is composed of approximately 0.008 percent nickel with the actual percentage composition varying according to the type of rock present in the crust. The natural concentration of nickel in soils usually ranges from 5 to 500 ppm, but soils derived from serpentine rock may contain levels as high as

6,000 ppm (National Academy of Sciences, 1975; Vaneslow, 1966). Various researchers (Whitby et al., 1978; Dudas and Pawluk, 1977; Frank et al., 1976; Mills and Zwarich, 1975; Hutchinson et al., 1974) have measured natural levels of nickel in soils at concentrations ranging from 1 ppm to 50 ppm. The average level of nickel in soil is estimated at approximately 50 ppm (Bowen, 1979; Aubert and Pinta, 1977). These data are presented in Table 3-5.

Anthropogenic inputs of nickel to soils are hypothesized to occur through several mechanisms: (a) emissions from primary smelters and metal refineries that are deposited on soils near the facility; (b) disposal of sewage sludge on soils or application of sewage sludge as a fertilizer; (c) auto emissions deposited on soils in the vicinity of the roadway; (d) emissions from electric power utilities deposited on soils downwind of the facility; (e) municipal waste incineration emissions deposited on soils; and (f) emissions from coal and oil combustion for water and space heating deposited on soils. The most significant anthropogenic nickel inputs to soil result from metals smelting and refining operations and sewage sludge applications (Hutchinson et al., 1981).

Table 3-6 presents data on nickel concentrations in soils resulting from anthropogenic inputs. The highest levels are found in soils located near nickel smelters and metal refineries. Concentrations of nickel up to 4,860 ppm have been measured in the surface litter of forested sites near smelting operations (Hutchinson et al., 1981). Frank et al. (1982) reported that aerial fallout from a nickel smelter resulted in the accumulation of nickel ranging from 600 to 6,455 ppm in the organic soil of a farm. At sites near metal refineries, recorded levels of nickel have been as high as 24,000 ppm. Generally, the concentrations of nickel in soils decrease with increasing distance from the emission point (Hutchinson et al., 1981; Hutchinson and Whitby, 1977; Ragaini et al., 1977; Beavington, 1975; Burkitt et al., 1972; Goodman and Roberts, 1971).

Soils in agricultural areas can receive anthropogenic enrichments of nickel when sewage sludge is applied to the land. Nickel has been identified as one of the trace metals found in sewage sludge that is likely to cause toxicity problems in plants (Webber, 1972). In sludge from more than 300 sewage treatment plants studied by Page (1974), the recorded nickel concentrations ranged from 10 to 53,000 ppm for dried sludge. The typical nickel concentrations in soils where sludge has been applied are significantly lower than those levels in the sludge itself. The amount of nickel in sludge-mixed soil is variable and appears to be dependent upon the sludge source and amount applied (Wollan and

TABLE 3-5. NATURAL LEVELS OF NICKEL IN SELECTED SOIL TYPES

Soil Description	Nickel Concentration (mg/kg, dry weight)	Reference
Loams and clays	90 - 100	Aubert and Pinta (1977)
Temperate and boreal regions	4 - 600	Aubert and Pinta (1977)
Arid and semiarid regions	50	Aubert and Pinta (1977)
Tropical humid regions	1 - 500	Aubert and Pinta (1977)
Serpentine	400 - 6,000	Vaneslow (1966)
Cultivated (various Canadian sites)	9 - 32	Whitby et al. (1978)
	27 - 42	Whitby et al. (1978)
	15 - 18	Whitby et al. (1978)
	12 - 22	Whitby et al. (1978)
	19 - 31	Whitby et al. (1978)
	20 - 35	Whitby et al. (1978)
Cultivated muck	15	Hutchinson et al. (1974)
Cultivated mineral	20	Hutchinson et al. (1974)
Virgin muck	8 - 15	Hutchinson et al. (1974)
Sandy agricultural	8	Frank et al. (1976)
Clay agricultural	28	Dudas and Pawluk (1977)
Organic agricultural	29	Dudas and Pawluk (1977)
Cultivated, poorly-drained	6 - 8	Dudas and Pawluk (1977)
Cultivated, well-drained	1 - 7	Dudas and Pawluk (1977)

TABLE 3-6. NICKEL CONCENTRATIONS IN ENRICHED SOILS

Enrichment Source	Nickel Concentration (mg/kg, dry weight)	Reference
Nickel smelter emissions	300 - 500	Rutherford and Bray (1979)
	to 4,860	Hutchinson et al. (1981)
Metal refinery emissions	to 24,000	Hutchinson et al. (1981)
Sewage sludge application	129	Chaney et al. (1977)
	2 - 50	Page (1974)
Auto emissions	1 - 8	Lagerwerff and Specht (1970) Hutchinson (1972)

Beckett, 1979). Heavy metal concentrations in sewage sludge and in soils from sites where sludge was applied have been studied by Chaney et al. (1977) for 43 treatment plants. The mean concentration of nickel in sludge-treated soil was measured at 129 ppm, with a median value of 42 ppm. Page (1974) measured nickel in sludge-amended soils at concentrations ranging from 2 to 50 ppm.

Auto emissions can result in the enrichment of soils with nickel. Lagerwerff and Specht (1970) studied the contamination of roadside soils near two major highways. Measured nickel concentrations were found to range from 0.90 to 7.4 ppm. These concentrations were lower at greater distances from traffic and at greater soil profile depths. Hutchinson (1972) conducted similar studies of nickel enrichment of soils by auto emissions and found levels of nickel as high as 32 ppm.

3.5.2 Nickel in Plants

The primary route for nickel accumulation in plants is through root uptake from soil. Nickel is present in vegetation usually below the 1 ppm level, except for plants grown in nickel-rich substrates such as serpentine soils. Concentrations ranging from 0.05 ppm to 5 ppm have been reported for cultivated crops and natural vegetation (Vaneslow, 1966). Connor et al. (1975) have reported mean values of approximately 0.20 to 4.5 ppm for nearly 2,000 samples of cultivated crops and natural vegetation. This study showed that although nickel levels in plants rarely exceeded 5 ppm, concentrations as high as 100 ppm could be measured in plants from serpentine soils.

Several researchers have attempted to assess the accumulations of nickel in plants grown in soils receiving anthropogenic enrichments of nickel (see Table 3-7). For crops grown in soils where sewage sludge was applied, the concentration of nickel was found to range from 0.3 to 1,150 ppm (Schauer et al., 1980; Mitchell et al., 1978; Clapp et al., 1976; Giordano and Mays, 1976; Anderson and Nilsson, 1972; LeRiche, 1968). Higher concentrations occurred in soils with low pH. A study by Beavington (1975) showed that concentrations of nickel in lettuce grown in soil near a copper smelter ranged from 2.7 to 6 ppm.

In a study on the uptake of nickel by the edible portions of food crops such as bush beans, cabbage, onions, tomatoes, and potatoes grown in test pots in municipal sludge from Ithaca, N.Y., Furr et al. (1976) observed: (1) at first-year harvest, nickel levels in the above food crops were increased 2- to

TABLE 3-7. ACCUMULATION OF NICKEL IN PLANTS

Growth Environment	Plant Species	Ni Concentration (mg/kg, dry weight)	Reference
Background	Cultivated crops Natural vegetation	0.05 - 5	Vaneslow (1966)
	Cultivated crops Natural vegetation	0.20 - 4.5	Connor et al. (1975)
Sludge enrichment			
66 Mg/ha/yr	Leeks, Beets	7 - 16.5	Le Riche (1968)
9 kg/ha	Rape	9.2	Anderson and Nilsson (1972)
42 - 165 kg/ha	Corn	0.3 - 3.0	Clapp et al. (1976)
24 Mg/ha	Various crops	0.8 - 76 in fruit, root 1.8 - 6.2 in leaves	Giordano and Mays (1976)
20 Mg/ha	Lettuce, Tomatoes	6 - 10	Schauer et al. (1980)
60 Mg/ha	Lettuce, Tomatoes	3 - 7	Schauer et al. (1980)
20 Mg/ha	Radishes, Carrots	5 - 11	Schauer et al. (1980)
60 Mg/ha	Radishes, Carrots	11 - 18	Schauer et al. (1980)
Soil pH 5.7	Lettuce, Wheat grain	1.7 - 241 119 - 1,150	Mitchell et al. (1978)
Soil pH 7.5		1 - 23 5 - 166	
Copper smelter inputs	Lettuce	2.7 - 6	Beavington (1975)

3-fold compared to control soil crops, the corresponding soil pH levels being 7.1 for sludge-amended samples and 5.3 for control soils; (2) at second harvest, the increases seen in the first harvest did not recur, except for about a 2-fold increase in onions and tomatoes.

As discussed previously (Frank et al., 1982), aerial fallout from a nickel smelter resulted in accumulation of nickel ranging from 600 to 6,455 mg/kg in the organic soil of a farm. Vegetables have been grown commercially for 20 to 40 years on this farm located 1 km (0.6 miles) from the smelter and in direct line with the prevailing winds. To evaluate the possible impact of nickel contamination on the soil, the nickel content of the edible parts of crops grown on this soil was determined. Nickel levels (mg/kg, dry weight) ranged from 80 to 280 in beet roots, 76 to 400 in cabbage heads, 15 to 395 in celery tops, 22 to 130 in lettuce tops and 24 to 140 in radish roots.

3.5.3 Nickel in Food

Nickel may be ingested by humans through the consumption of nickel which has accumulated in plants used as foods. Some representative values for various foodstuffs, adapted from studies by Schroeder et al. (1962), Vaneslow (1966) and, more recently, Nielsen and Flyvholm (1984) are given in Table 3-8. The level of nickel rarely exceeds 1 ppm, but in some specialty foods, such as soya beans and cocoa, it has been measured as high as 5.2 and 9.8 ppm, respectively.

Food processing methods may add to the nickel levels naturally present in foodstuffs by (1) the leaching of nickel from food-processing equipment made from stainless steel, (2) the milling of flour, and (3) the catalytic hydrogenation of fats and oils with nickel catalysts (National Academy of Sciences, 1975). Daily nickel intake may also become elevated after the replacement and supplementation of specialty items, such as soya beans and chocolate, in the average diet. Calculations show that nickel intake may reach levels as high as 900 µg Ni/day through such means (Nielsen and Flyvholm, 1984).

3.5.4 Nickel in Cigarettes

Cigarette smoking may contribute to man's daily nickel intake by inhalation. Early studies suggested that nickel in mainstream smoke was in the form of carbonyl (Szadkowski et al., 1970; Sunderman and Sunderman, 1961); however, recent data have not supported these earlier findings (Alexander et al., 1983). The amount of nickel in mainstream smoke is a topic of some controversy and

TABLE 3-8. NICKEL CONTENT OF VARIOUS CLASSES OF FOODS IN U.S. AND DANISH DIETS

Food Class and Examples	Nickel Content, ppm, wet weight
Grains/grain products	
Wheat flour, all-purpose	0.54
Bread, whole-wheat	1.33
Corn, fresh frozen	0.70
Rice, polished American	0.47
Rice	0.33[a]
Rye flour	0.23
Rye bread	0.21
Oatmeal	1.20[a]
Fruits and vegetables	
Potatoes, raw	0.56
Peas, fresh frozen	0.30
Peas, canned	0.46
Peas	0.37[a]
Beans, frozen	0.65
Beans, canned	0.17
Soya beans	5.20[a]
Lettuce	0.14
Cabbage, white	0.32
Tomatoes, fresh	0.02
Tomato juice	0.05
Spinach, fresh	0.35
Spinach	0.06[a]
Celery, fresh	0.37
Apples	0.08
Bananas	0.34
Pears	0.20
Hazel nuts	1.90[a]
Seafood	
Oysters, fresh	1.50
Clams, fresh	0.58
Shrimp	0.03
Scallops	0.04
Crabmeat, canned	0.03
Sardines, canned	0.21
Haddock, frozen	0.05
Swordfish, frozen	0.02
Salmon	1.70

(continued on following page)

TABLE 3-8 (continued)

Food Class and Examples	Nickel Content, ppm, wet weight
Meats	
Pork (chops)	0.02
Lamb (chops)	Not detected
Beef (chuck)	Not detected
Beef (round)	Not detected
Chocolate	
Cocoa	9.80[a]
Milk chocolate	0.57[a]
Dark chocolate	1.80[a]

[a] Value is that of Danish diet.

Source: Adapted from National Academy of Sciences (1975) and Nielsen and Flyvholm (1984).

further research is needed before definitive conclusions can be reached (see Chapter 4).

3.6 GLOBAL CYCLE OF NICKEL

Nickel in all environmental compartments (air, water, and soil) is continuously transferred between these media by natural chemical and physical processes such as weathering, erosion, runoff, precipitation, stream/river flow, and leaching. The ultimate sink for nickel is the ocean. The cycle is continuous, however, because nickel may leave the ocean as sea spray aerosols, burst, and release minute particles containing nickel and other elements into the atmosphere. These particles can serve as nuclei for the condensation of rain and snow, thereby reintroducing nickel into the global cycle. Nickel introduced into the environment by anthropogenic means is subject to the same physical and chemical properties affecting naturally occurring nickel, and accounts for increased ambient nickel concentrations in all environmental media.

In the atmosphere, nickel-containing particulates are subject to dispersion and transport by winds, and can be transferred from the atmosphere to soil or water by wet or dry deposition, impaction, or gravitational settling. In water bodies, nickel is transported by stream flow and can be removed from the water column by sedimentation, precipitation from solution, or adsorption onto suspended solids. In soils, nickel may be sorbed by clay or mineral fractions, complexed with organic material, or leached through the soil column into the groundwater. Cross-media transfer between soil and water occurs via erosion and runoff. Ultimately, nickel will be deposited in the world's oceans.

This section briefly examines the mechanisms by which nickel is cycled through all environmental media, and where possible, the amount of nickel entering each compartment from natural and anthropogenic sources is quantified.

3.6.1 Atmosphere

Nickel is introduced into the atmosphere from both natural and anthropogenic sources, as shown in Figure 3-3. Estimates of the portion of the total atmospheric burden of nickel attributed to either source category vary, depending on the choice of emission rate and nickel concentration of the material being dispersed. Nriagu (1980) estimated that 2.6×10^4 Mg (2.9×10^4 tons) of nickel are released into the atmosphere per year, worldwide from natural sources, and that anthropogenic sources account for another 4.7×10^4 Mg (5.2×10^4 tons).

Galloway et al. (1982) estimated similar global emissions from natural sources, 2.8×10^4 Mg (3.1×10^4 tons)/year, but report emissions from anthropogenic sources of 9.8×10^4 (1.1×10^5 tons)/year, an estimate nearly twice that reported by Nriagu. The discrepancy is most likely due to the choice of emission factors. The proportion contributed to the atmosphere by natural sources varies with local meteorological conditions, soil type, and physical factors. Erosion by wind and volcanic action contributed an estimated 40 to 50 percent of the airborne nickel from natural sources (Nriagu, 1980). Other natural sources include forest fires, sea salt spray, meteoric dust, and vegetative exudates (Schmidt and Andren, 1980). Up to 80 percent of anthropogenic emissions of nickel may be generated by fossil fuel combustion and nonferrous metals production (Nriagu, 1980). Other researchers have estimated that combustion of oil alone accounts for 83 percent of atmospheric nickel from anthropogenic sources (Lee and Duffield, 1979). Although the resolution of differences in these worldwide emissions is beyond the scope of this document, it seems apparent that combustion and other high temperature processes (metallurgical furnaces) account for a significant portion of industrially generated nickel in the atmosphere. As discussed elsewhere in this chapter, most anthropogenic

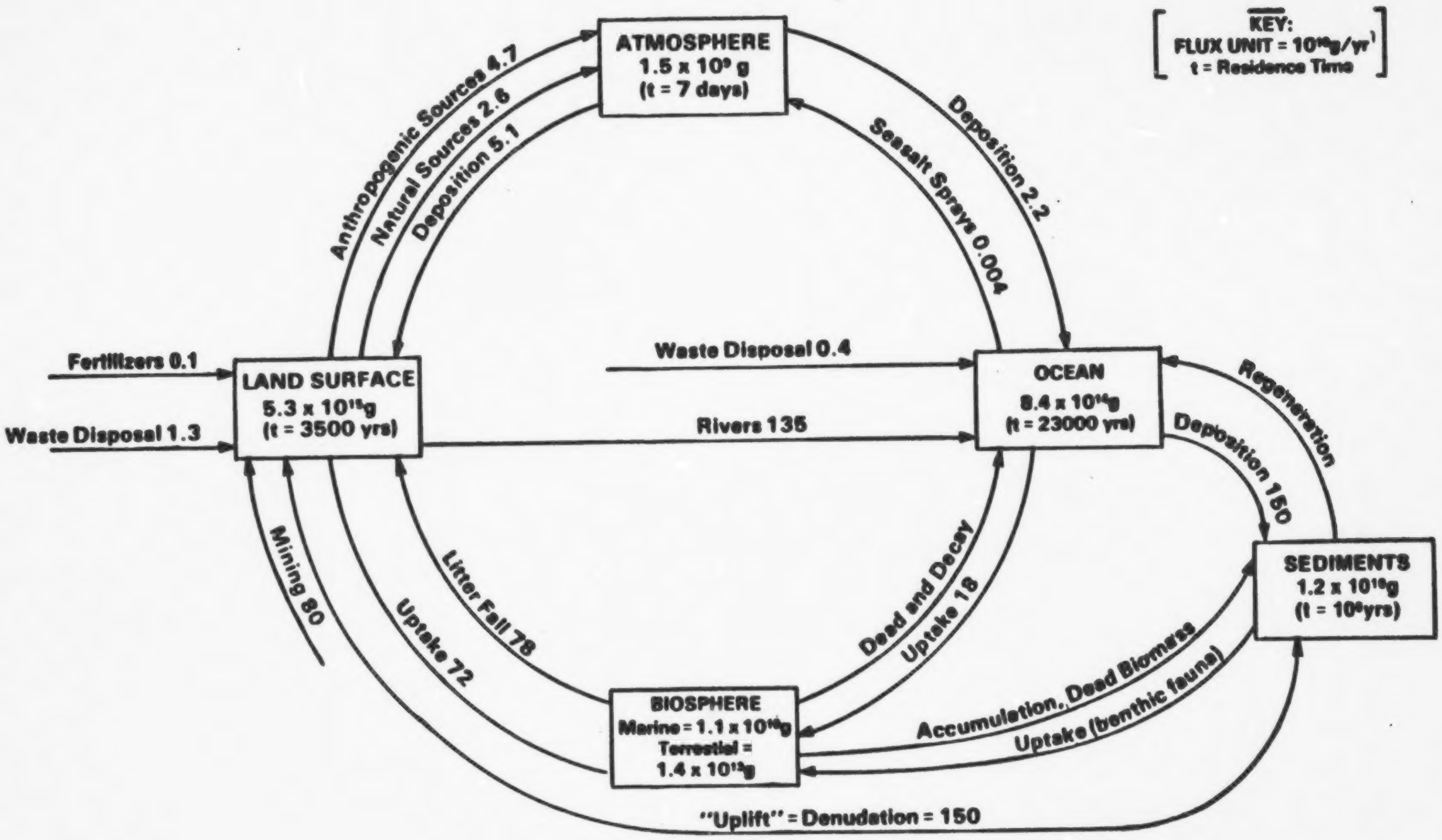
KEY:
FLUX UNIT = 10^{10}g/yr^{1}
t = Residence Time
ATMOSPHERE
1.5×10^9 g
(t = 7 days)
Anthropogenic Sources 4.7
Natural Sources 2.6
Deposition 5.1
Deposition 2.2
Seasalt Sprays 0.004
Fertilizers 0.1
Waste Disposal 1.3
LAND SURFACE
5.3×10^{15}g
(t = 3500 yrs)
Waste Disposal 0.4
Rivers 135
OCEAN
8.4×10^{14}g
(t = 23000 yrs)
Regeneration
Deposition 150
SEDIMENTS
1.2×10^{18}g
(t = 10^8yrs)
Mining 80
Uptake 72
Litter Fall 78
Dead and Decay
Uptake 18
BIOSPHERE
Marine = 1.1×10^{10}g
Terrestial =
1.4×10^{13}g
Accumulation, Dead Biomass
Uptake (benthic fauna)
"Uplift" = Denudation = 150

Figure 3-3. The global cycle of nickel on a 1-year frame.
Source: Nriagu (1980)

nickel is likely to be present as the soluble sulfate, with additional amounts present as various oxides and silicates of nickel.

Once nickel enters the atmosphere, it may remain suspended and available for transport or it can be removed by wet or dry deposition. A residence time in the atmosphere of 5.4 to 7.9 days has been estimated for nickel (Schmidt and Andren, 1980). Based on mathematical models, the proportion of nickel removed by wet and dry deposition are about equal in areas receiving 0.5 m (19.7 in.) rain per year (Schmidt and Andren, 1980).

The size of the particle influences the type of deposition by which it is removed from the atmosphere. Fine particulates and gases tend to move higher into the troposphere and become incorporated into raindrops (Galloway et al., 1982). Larger particles are more subject to gravitational settling near the emission source.

Davidson (1980) applied three dry deposition models to ambient data from six U.S. cities and calculated a dry deposition flux for nickel of 1 to 2.7 ng/cm^2 per day, with deposition velocities ranging from 0.19 to 0.49 cm/sec. The mass median diameter of particles used in these analyses was between 1.05 and 1.52 μm. Galloway et al. (1982) reported wet deposition rates of 2.4 to 114 μg/l nickel in urban areas (median 12 μg/l). Their analyses showed that dry deposition accounted for 30 to 60 percent of total or bulk deposition of nickel, similar to the results of Schmidt and Andren (1980).

Either method of deposition can return atmospheric nickel-containing particulate to the earth's surface. Nriagu (1980) estimated a total atmospheric fallout of 2.2×10^4 Mg (2.4×10^4 tons) nickel per year are received by ocean waters and 5.1×10^4 Mg (5.6×10^4 tons) are deposited on land. Of the material deposited on land masses, a fraction falls on surface waters, thereby subjecting nickel to additional fate and transport mechanisms of both aquatic and soil/sediment media.

3.6.2 Water

Nickel is introduced into fresh waters by natural and anthropogenic means. Natural sources include both wet and dry deposition of airborne nickel-containing particulates, erosion (weathering), and runoff; direct discharges from industrial facilities account for input from anthropogenic sources. The distinct definitions of natural and anthropogenic sources may become less clear, however, considering that natural removal processes such as rainout are removing nickel-containing material that was introduced into the atmosphere by industrial activity.

In areas relatively free from man's influence, the concentrations of nickel in surface and groundwaters are low and are usually a result of the weathering of parent rock or soil (Snodgrass, 1980; National Academy of Sciences, 1975). The ambient data presented in this chapter show that most river basins have comparatively low concentrations of nickel in surface and groundwater, with elevated concentrations seen in heavily industrialized areas such as the Ohio River basin.

Once in the aquatic environment, nickel may be transported by bed traction or water flow in the dissolved or adsorbed form. In the major rivers of the world, Snodgrass (1980) noted the following distribution of forms of nickel transported:

- 0.5 percent in solution
- 3.1 percent adsorbed
- 14.9 percent associated with organic matter
- 34.4 percent as crystalline material (presumably weathered minerals)
- 47 percent as a precipitated coating on particles

This distribution is determined for each specific location by water pH, pE, ionic strength, concentration of organic and inorganic ligands, and the presence of surfaces to which nickel tends to sorb (hydrous iron oxides). Sibley and Morgan (1975) described a fresh water system using specific water quality parameters and ligand concentrations and entered these data into a speciation model. Model output showed that the carbonate complex was the major dissolved species followed by the free ion and the hydroxide. Adsorption was the second most significant fate process. Unfortunately, the model did not include organic ligands, known to substantially affect the mobility of nickel. Nevertheless, this model provides an indication of the species of nickel likely to be found in fresh waters.

Nickel in fresh water, either dissolved or adsorbed to sediments, eventually is deposited in the oceans which are the ultimate sink for the metal. About 1.4×10^6 Mg (1.5×10^6 tons) nickel/year enter world oceans as riverine suspended particulate (Nriagu, 1980), with an additional 1.1×10^4 Mg (1.2×10^4 tons)/year input from rivers as dissolved nickel. Industrial and municipal wastes may contribute 3.8 x 10^3 Mg (4.2 x 10^3 tons) nickel/year (Nriagu, 1980), 80 percent of which is estimated to be soluble forms of the metal (Snodgrass, 1980).

The transport of nickel to the oceans depends on stream velocity, channel configuration, and stream water quality. Although nickel tends to exist in the dissolved state, some of the metal does sorb to suspended particulates in the stream. The degree to which nickel is sorbed is a function of pH and the presence or absence of ligands. Depending on stream flow, the sorbed nickel may settle in sediment beds, impact on geologic channel features, or be transported through the river system by bed traction, eventually reaching the ocean. Dissolved nickel is transported by stream flow.

Nickel transported adsorbed to particles in river systems may be desorbed when entering estuarine and subsequently marine waters. Using their model, Sibley and Morgan (1975) predicted that in seawater, the free ion was the major species, followed by dissolved nickel chloride and hydroxide. Adsorption of nickel decreases with the increasing ionic strength of seawater.

Not all nickel in seawater remains suspended, as an estimated residence time for nickel in the deep ocean is 2.3 x 10^4 years (Nriagu, 1980). Nickel may be taken up by marine flora and fauna or deposited in oceanic muds and sediments. Accumulation of the metal in these sediments, the ultimate sink for nickel, is estimated to exceed 1.5 x 10^6 Mg (1.7 x 10^6 tons)/year (Nriagu, 1980). The residence time for nickel in sediments is on the order of 10^8 years (Nriagu, 1980).

3.6.3 Soil and Sediments

Nickel is a naturally occurring constituent of several classes of rock, and may enter the soil by chemical and physical degradation of parent rock (Boyle, 1981). Industrial activities are additional sources of nickel in soils through both direct means (land spreading of sewage sludge) and indirect pathways (deposition of airborne particulates containing nickel generated by industrial operations). Nriagu (1980) estimated that on a worldwide basis, 5.1 x 10^4 Mg (5.6 x 10^4 tons) of nickel are introduced into the soil environment each year by deposition of atmospheric nickel-containing particulates, and that waste disposal (sewage sludge, fly ash) and fertilizers add 1.4 x 10^4 Mg and 1 x 10^3 Mg (1.5 x 10^4 and 1.1 x 10^3 tons), respectively. Litter fall from vegetation may provide an additional 7.8 x 10^5 Mg (8.6 x 10^5 tons) of nickel on an annual basis (Nriagu, 1980).

Nickel added to soils is subject to transport by erosion and runoff, which carry nickel through river systems and estuaries to the ultimate sink, the ocean. Nickel may also migrate through the soil column, concentrating in a given soil layer depending on the chemical characteristics of the soil. If the soil is permeable and no sorbing matter is present, nickel can enter groundwater supplies by leaching through the soil column.

The extent to which nickel is held in the uppermost soil layers or migrates through the soil depends on soil pH, amount of precipitation, and the presence of substances which may sorb nickel. The form of nickel input into soil (i.e., atmospheric deposition of a complex nickel-iron oxide or direct discharge of nickel-containing mine wastes) affects nickel mobility as well. Soils rich in organic material and hydrous iron and manganese oxides can immobilize nickel as the metal sorbs to these materials. However, below pH 6.5 the iron and manganese oxides break down, thereby remobilizing any nickel present (Rencz and Shilts, 1980). Hutchinson et al. (1981) report increased nickel concentrations in organic surface soil layers in areas up to 48 km (30 miles) from refineries and smelters, presumably because of the high cation exchange capacity of the organic material. The organo-nickel complexes can serve to reduce the availability of nickel for further transport.

Insoluble or less soluble nickel species may deposit and add to riverbed sediment loads as nickel is transported in rivers and streams. Soluble nickel may also be sorbed to sediments, with fine sediments (clays) tending to sorb more nickel than coarse fractions like sand (Hutchinson et al., 1981). In either form nickel is ultimately deposited in the oceans.

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4. NICKEL METABOLISM IN MAN AND ANIMALS

4.1 ROUTES OF NICKEL ABSORPTION

The major routes of nickel absorption are inhalation and ingestion via the diet, with percutaneous absorption a less significant factor for the systemic effects of nickel but important in the allergenic responses to nickel. Parenteral administration of nickel is of interest to experimental studies and is particularly helpful in assessing the kinetics of nickel transport, distribution, and excretion. Parenteral exposure of humans to nickel from medications, hemodialysis, and protheses can also be a significant problem to certain sectors of the population. Transplacental transfer to the fetus is of importance in the assessment of _in utero_ effects. The relative magnitudes of nickel intake and absorption in humans are briefly summarized in the final portion of this section.

The amounts of nickel absorbed by organisms are determined not only by the quantities inhaled or ingested, but also by the chemical and physical forms of nickel. A number of _in vitro_ studies have described the relationship of chemical composition and such properties as crystallinity of nickel compounds to their relative solubility in biologically relevant media. In the most comprehensive study of this type, Kuehn and Sunderman (1982) determined dissolution half-times of 17 nickel compounds in water, rat serum, and renal cytosol. The potent carcinogen, nickel subsulfide, had a dissolution half-time of 34 and 21 days in serum and kidney cytosol, respectively. By comparison, elemental nickel, nickel oxide, and β-nickel sulfide had corresponding half-times of 1.4 to 11 years. In general, half-times were less in biological systems than in water.

While _in vitro_ solubilization half-times determined in this manner are useful to know, they must be cautiously used in predicting _in vivo_ solubility. Furthermore, examination of the solubilization half-times for all 17 nickel forms in the Kuehn and Sunderman study indicates that solubilization cannot be the only factor operating in the carcinogenicity of various nickel compounds.

In a related study, Ung and Furst (1983) reported that dissolution of nickel powder in human serum reached a rate of approximately 23 mg Ni/l serum at 48 hours with shaking of the suspension. This rate of dissolution was much greater than that in water, saline, or ethylenediamine tetraacetate chelant solution.

A direct comparison of the Ung and Furst data with data for metallic nickel described in the Kuehn and Sunderman (1982) study as a means of comparing species-variable serum solubilization of metallic nickel is, unfortunately, not possible because of differences in data presentation. In addition, the reliability of the analytical method used by Ung and Furst is questionable in that the serum blanks were reported to contain 3 mg Ni/l, which is approximately 1000-fold higher than generally accepted values.

Lee and co-workers (1983) found that 1 to 10 mM levels (59 to 590 mg/l) of nickel II in a biological solution were obtained after incubation of α-nickel subsulfide in a mixture of DNA, rat liver microsomes, and NADPH. Nickel was bound to DNA, with binding mediated by microsomal protein. Suppression of the dissolution rate by the reductant NADPH indicates that oxidation of the subsulfide nickel is central to solubilization, which supports earlier data of Kasprzak and Sunderman (1977).

In the more complex in vitro cellular test systems, where the end point is relative phagocytosis of nickel compounds as a prelude to cell transformations, Costa and Mollenhauer (1980) have furnished evidence to show that carcinogenicity of particulate nickel compounds is directly proportional to the rate of cellular uptake. Such uptake is clearly related to the relative negative charge density on particulate surfaces (Heck and Costa, 1982). Crystalline nickel monosulfide has a negative surface charge, is actively taken up by cells, and is a potent carcinogen. The amorphous form of the sulfide has a positive charge, is not sequestered, and is noncarcinogenic. Chemical surface reduction of the amorphous form, using a metal hydride, greatly enhances phagocytosis and cell transformation induction (Heck and Costa, 1982).

Factors other than the chemical and physical properties of nickel, such as host organism nutritional and physiological status, may also play a role in nickel absorption, but they have been little studied outside of investigations directed at an essential role for nickel.

4.1.1 Nickel Absorption by Inhalation

Respiratory absorption of various forms of nickel is probably the major route of nickel entry into man under conditions of occupational exposure, and considerable attention has been given to nickel inhaled as either the highly toxic nickel carbonyl or nickel particulate matter.

Nickel carbonyl, $Ni(CO)_4$, is a volatile, colorless liquid (b.p. 43°C). Armit (1908) found its relative toxicity to be 100-fold that of carbon monoxide. Its presence and toxicological history as a workplace hazard followed closely upon the development of the Mond process of nickel purification in its processing (Mond et al., 1890). A detailed discussion of the toxicological aspects of nickel carbonyl poisoning is included in the National Academy of Sciences report on nickel (National Academy of Sciences, 1975) as well as a review by Sunderman (1977).

Studies of nickel carbonyl metabolism by Sunderman and co-workers (Sunderman and Selin, 1968; Sunderman et al., 1968) indicate that pulmonary absorption is both rapid and extensive, with the agent passing the alveolar wall intact. Sunderman and Selin (1968) observed that rats exposed to nickel carbonyl at 100 mg Ni/l air for 15 minutes excreted 26 percent of the inhaled amount in the urine by 4 days postexposure. Taking into account the exhaled quantity, as much as half of the inhaled amount could have been initially absorbed.

Few data exist on the pulmonary absorption of nickel from particulate matter deposited in the human lung. The International Commission on Radiological Protection (ICRP) Task Group on Lung Dynamics (1966) has advanced detailed deposition and clearance models for inhaled dusts of various chemical origins as a function of particle size, chemical properties, and compartmentalization within the pulmonary tract. While these models have limitations, they can be of some value in approximating deposition and clearance rates for nickel compounds of known particle size. For example, Natusch et al. (1974), based on a detailed study of eight coal-fired power plants, found that nickel is one of a number of elements emitted from these sources that is found in the smallest particles of escaped fly ash, approximately 1 to 2 μm mass median aerodynamic diameter (MMAD), this being a size that penetrates deepest into the pulmonary tract. According to the approaches of the ICRP model, particles of 1 μm undergo a total deposition of 63 percent, with 30 percent in the nasopharyngeal tract, 8 percent in the tracheobronchial part, and 25 percent in the pulmonary compartment. The clearance rate of deposited particulate matter in the ICRP model is based on chemical homogeneity of the particulates, however, and one can only approximate such clearance if heterogeneous particles are considered. According to Natusch et al. (1974), nickel-enriched particles in fly ash have much of the nickel on the particle surface. If one approximates the clearance rate by assuming that particles enriched in nickel in the outer portions of the particle are handled by the model lung in a fashion similar to a homogeneous particle, then one obtains a total absorption (clearance) of approximately 6 percent, with major clearance, 5 percent, calculated as taking place from the pulmonary compartment.

Further complicating the issue of pulmonary absorption from particulate matter is the finding of Hayes et al. (1978) that trace elements such as nickel are not uniformly distributed among particles of similar size. From scanning electron microscope studies, the authors found that some particles carry much of the element for a given concentration as determined by ordinary chemical analysis. Therefore, theories relating lung clearance to estimates of toxicity, based on bulk analysis rather than on single-particle analysis, must be carefully considered.

Quantitative data for the actual uptake of particulate nickel from the various compartments of the human respiratory tract are meager. Kalliomäki and co-workers (1981) observed very little increase over time in urinary nickel in stainless steel welders, even when the nickel content of inhalable welding fumes approached 1 percent and the nickel concentration ranged up to 30 µg Ni/m^3. The authors' observations indicated that very little nickel is absorbed from the respiratory tract.

Torjussen and Andersen (1979) found that nickel accumulation in nasal mucosa of nickel workers was highest with inhalation of particulate subsulfide and oxide forms as compared to inhalation of nickel chloride/sulfate aerosols. This finding would be expected on the basis of the relative solubility of the respective compounds. Nasal mucosal nickel underwent very slow clearance, having a half-life of about 3.5 years.

Animal studies have provided more quantitative information on the deposition and absorption rates of various forms of nickel in the lung.

Wehner and Craig (1972), in their studies on the effect of nickel oxide aerosols on the golden hamster, observed that inhalation by these animals of nickel oxide particles in a concentration of 2 to 160 µg/l (2 to 160 mg/m^3) and particle size of 1.0 to 2.5 µm MMAD led to a deposition of 20 percent of the total amount inhaled. Six days postexposure, 70 percent of the nickel oxide remained in the lungs, and even after 45 days approximately half the original deposition was still present. Since no material increase in nickel levels of other tissues had occurred, it appeared that absorption in this interval was negligible. It is possible that the relatively high exposure concentrations used may have affected lung clearance mechanisms and led to a decrease in lung clearance of particles (see Section 5.2.2). In a later, related study (Wehner et al., 1975), co-inhalation of cigarette smoke showed no effect on either deposition or clearance.

Kodama and co-workers (1985) exposed adult rats to nickel oxide aerosol (MMAD range, 0.6 to 4.0 μm) at a concentration of 0.4 to 70 mg/m^3 for a maximum period of 90 days (6 to 7 h/d, 5 d/wk). In addition to an exposure-lung deposition relationship, deposition was observed to be inversely related to particle diameter, from 24 to 2.3 percent. No significant absorption of nickel into the blood stream occurred as evidenced by the absence of nickel elevation in blood and soft tissues across the dosing groups. The authors estimated an annual elimination rate of the element from lungs of these animals at about 100 μg Ni/year.

Wehner et al. (1979) exposed Syrian hamsters to nickel-enriched fly ash aerosol (respirable concentration, approximately 185 to 200 μg fly ash/l) for either 6 hours or 60 days and found that, in the short exposure, about 90 percent of 80 μg deposited in the deep tract remained 30 days after exposure, indicating very slow elimination. In the two-month study, the deep tract deposition was approximately 5.7 mg enriched fly ash, or 510 μg nickel. Thus, nickel leaching from the nickel-enriched fly ash in the hamster's lung did not occur to any extent over the experimental time frame.

In a more recent study, Wehner et al. (1981) exposed hamsters to approximately 70 μg/l respirable nickel-enriched fly ash (NEFA) aerosol (6 percent nickel), 17 μg/l NEFA (6 percent nickel), or 70 μg/l fly ash (0.3 percent nickel) for up to 20 months. The authors observed a difference in nickel lung concentrations and suggested that the apparent increased retention of nickel in the high-NEFA group (731 μg after 20 months exposure compared to 91, 42, and 6 μg for the low-NEFA, FA, and control groups, respectively) was due to reduced pulmonary removal.

Leslie and co-workers (1976) have described their results from exposing rats to nickel and other elements contained in welding fumes. In this case, the particle size versus nickel content was known precisely, highest nickel levels being determined in particles 0.5 to 1.0 μm in diameter at an air level of 8.4 μg Ni/m^3. While the authors did not determine the total nickel deposition in the lungs of these animals, they observed that essentially no elimination of the element from the lung had occurred within 24 hours, nor were there elevations in blood nickel, suggesting negligible absorption.

In a related study of Kalliomäki et al. (1983b), the authors observed a rough linear relationship of lung nickel levels with inhalation exposure in rats exposed to a stainless steel welding fume. When the relative nickel content of the fume was 0.4 percent, the measured nickel retention rate was 0.3 μg Ni/g dried lung tissue/hour of inhalation, and the maximum level was 7.1 μg Ni/g dried lung tissue. The half-time of nickel elimination from the lungs of these animals was 30 ± 10 days.

Kalliomäki and co-workers (1983a) also demonstrated, in experimental animals, that the deposition and elimination rate for nickel from welding fumes is highly dependent on the type of welding process. Fumes from stainless steel welding, in which the metal inert gas method is used, were compared to fumes generated from manual metal arc systems. The nickel retention rate in the lung was increased approximately 20-fold when animals were exposed to fumes from the former process (6.1 versus 0.29 μg/g/h). A corresponding maximum lung nickel level (130 versus 7.1 μg/g) of 20:1 was obtained, and a corresponding 3-fold increase in nickel half-time clearance (86 versus 30 days) was observed.

From this study, it would appear that the inert gas method of welding poses a greater nickel exposure risk than does the conventional technique. Since the authors did not characterize particle size profiles or nickel content versus size, it is not possible to define the basis of these differences.

Srivastava et al. (1984) reported that exposure of adult rats (6 h/d, 15 days) to fly ash generated at a coal-fired power plant (0.2 to 0.4 mg/l, 400 mesh) was associated with a steady rise in nickel content of lung, liver, heart, kidney, small intestine, and serum. The relative rates of decay of nickel levels in these tissues were measured up to 30 days following the last day of exposure. The biological half-time for nickel in the lung was calculated to be 21 days. The corresponding values for the extrapulmonary organs were: 26 (liver), 5.5 (heart), 8 (kidney), 30 (small intestine), and 57 days (serum). While the extent of nickel leaching from fine-particle fly ash cannot be estimated from this study, it nevertheless serves to indicate that the element in this material was sufficiently bioavailable in the lung to lead to marked elevations of nickel in various vital tissues.

In contrast to these studies with particulates, Graham et al. (1978), using mice and nickel chloride aerosol (≤ 3 μm diameter, 110 mg Ni/m^3), found about 75 percent elimination by day 4 postexposure. The rapid elimination of the nickel halide was probably due to its solubility relative to the oxides or other insoluble nickel forms in welding fumes.

The implications of these studies in determining the relationship of pathogenic effects to respiratory absorption is somewhat unclear. While the above studies appear to demonstrate that differences in compound solubilities relate to pulmonary elimination, with inert compounds having relatively slower removal, the relationship of elimination to toxic manifestations is less certain. For example, in the Wehner et al. (1981) study on hamsters, the authors concluded that the quantity of dust, rather than its nickel content, appeared to be the major factor in determining tissue response. The severity of pathological findings was significantly higher ($p < 0.01$) in the FA and high-NEFA group (70 μg/l each) than in the low-NEFA group (17 μg/l), whereas the pathologic differences between the FA group (0.3 percent nickel) and the high-NEFA group (6 percent nickel) were insignificant despite the large differences in lung retention (_vide supra_). (For further discussion, see Chapter 8).

Several studies have examined the lung clearance rate for nickel when various compounds of the element were administered intratracheally to rats or mice. It is important to note that these various studies employed different nickel compounds that likely have different effects on elimination kinetics.

Corvalho and Ziemer (1982) administered microgram amounts of ^{63}Ni-labeled nickel chloride intratracheally to adult rats and observed that 71 percent of the administered amount was removed from the lungs by 24 hours, with only 0.1 percent remaining by day 21. This indicated a lung clearance half-time of soluble nickel of less than 24 hours in the rat, with the rate of urinary elimination of nickel paralleling that of nickel removal from lung.

Williams et al. (1980) also instilled ^{63}Ni-labeled nickel chloride solution in rats at levels of 1, 10, and 127 nmol nickel. Removal of nickel from rat lung was independent of instillation concentration with a nickel removal rate (percent) of 0.2/minute, corresponding to a calculated clearance half-time of approximately 4.5 hours. Williams et al. (1980) also studied the behavior of the perfused and ventilated rat lung using the same test protocol. In this case, clearance rate half-time was dose-dependent, being around 20 hours at the 1 nmol dose and decreasing to 4.6 hours at the 127 nmol dose.

Moderately soluble nickel carbonate was instilled intratracheally into mice at a loading of 50 μg in a study by Furst and Al-Mahraq (1981). From the authors' tabulated daily nickel urinary excretion rates (erroneously indicated in the report in mg/ml instead of μg/ml), a retention half-time of roughly 72 hours for the carbonate can be calculated. This assumes that urinary excretion parallels that of instilled nickel absorption from lung, which is clearly the case in the Corvalho and Ziemer (1982) report on rats.

In the study of English and co-workers (1981), where both ^{63}Ni-labeled nickel chloride solution and nickel oxide suspension were administered to rats via intratracheal instillation, the rather slow clearance of the oxide, also described in other studies, was associated with accumulation of the element in both mediastinal lymph nodes and lung. Raised lymph node levels indicate that lymphatic clearance is one route in the slow removal of oxide from the lung.

The pulmonary elimination of particulate ^{63}Ni-labeled nickel subsulfide in mice (1.7 μm, mass median diameter) has been described by Valentine and Fisher (1984). Following intratracheal instillation, elimination was observed in two distinct phases having biological half-times of 1.2 and 12.4 days, respectively. The label was detected in blood, liver, and other tissues by 4 hours post-instillation. In these experiments, approximately 57 percent of the total label was excreted after 3 days, and excretion was 100 percent after 35 days. The faster elimination rate (1.2 days) could be attributed to retro-ciliary removal of the material with translocation to the gastrointestinal tract, consistent with a significant level of label in feces during the first 12-hour period. Approximately 60 percent of the total label excreted was lost in urine, demonstrating a significant degree of solubilization of particulate subsulfide by the mouse lung. As described earlier, the data of Kuehn and Sunderman (1982) showed dissolution half-times for the subsulfide of 34 and 21 days in serum and tissue cytosol, respectively. Hence, both in vitro and in vivo bioavailability data suggest that there is a higher level of mobilization of the element in this form into the blood than might be expected based on simple kinetics of solubility.

In addition to nickel exposure in man due to inhalation of ambient and workplace air, cigarette smoking constitutes a possible exposure source among heavy smokers. Early studies by Stahly (1973), Szadkowski and co-workers (1970), and Sunderman and Sunderman (1961) indicated that 10 to 20 percent of cigarette nickel was carried in mainstream smoke, with better than 80 percent of this amount being in gaseous, rather than particulate, form. It was claimed that nickel carbonyl constituted the gaseous fraction (Sunderman and Sunderman, 1961), suggesting that the relative absorption of nickel from cigarette smoke was proportionately greater than from airborne nickel particulates, and in heavy smokers may have been the main source of inhalatory nickel absorbed.

Recent data indicate, however, that tobacco nickel in mainstream smoke is not in the form of the carbonyl. Using Fourier-transform infrared spectrometry and testing representative commercial cigarette samples via the "vacuum-smoking" method, Alexander et al. (1983) reported that no measurable amounts of nickel carbonyl could be found at a detection level of 0.1 µl carbonyl/l smoke. Another study showed that the amount of nickel in mainstream smoke from cigarettes with a high nickel content is low (Gutenmann et al., 1982). However, the tobacco used in this study was grown on sludge-amended soil which might have affected the pyrolytic behavior of the test leaf versus that of ordinary tobacco. Further research is needed on the topic.

In summary, available human and animal data permit the following conclusions about respiratory absorption of nickel:

(1) Insoluble particulate nickel, e.g., the oxide and the subsulfide, deposited in the various respiratory compartments in both occupationally exposed subjects and the general population, is very slowly absorbed with accumulation over time; nickel in the nasal mucosa of nickel workers has a clearance half-time of approximately 3.5 years. Workers who inhale nickel-containing welding fumes do not show increased systemic levels, indicating extremely low absorption of nickel from the lung.

(2) Experimental animal data using various species show very slow clearance of deposited and insoluble nickel oxide from the respiratory tract, moderate clearance of the carbonate with a half-time of around three days, and rapid clearance of soluble nickel salts with a half-time of hours to several days. In the case of nickel oxide, clearance from the lung involves both direct absorption into the blood stream and clearance via the lymphatic system.

4.1.2 Gastrointestinal Absorption of Nickel

Gastrointestinal intake of nickel by man is surprisingly high, relative to other toxic elements, which is at least partly accounted for by contributions of nickel from utensils and equipment in processing and home preparation of food.

Total daily dietary intake values may range up to 900 μg nickel, depending on the nature of the diet, with average values of 300 to 500 μg daily (National Academy of Sciences, 1975; Nielsen and Flyvholm, 1984). Collectively, the data of Horak and Sunderman (1973), Nodiya (1972), Nomoto and Sunderman (1970), Perry and Perry (1959), and Tedeschi and Sunderman (1957) indicate that 1 to 10 percent of dietary nickel is absorbed. In the more recent study of Christensen and Lagesson (1981), adult human volunteers ingested, without fasting, a single dose of 5.6 mg nickel as the sulfate. Over the three days after ingestion, urinary nickel levels rose to a peak and then decreased towards normal. The cumulative excretion over this time period was 176 μg, indicating a minimal gastrointestinal absorption rate of roughly 3 percent.

Fecal analysis more accurately reflects dietary intake where the rate of absorption is known and the existence and extent of biliary excretion is known. Diet profiles tend to differ from fecal analysis data owing to the obvious inherent difficulty of arriving at "true" diets for human subjects. In the case of nickel, where absorption is assumed to be small, the fecal analysis data approximate the low end of dietary profile estimates, and one can say that daily gastrointestinal intake is probably 250 to 300 μg Ni/day.

One question that arises in considering the dietary intake and absorption of toxic elements has to do with the bioavailability of the agent in solid foodstuffs versus water and beverages. Ho and Furst (1973) observed that intubation of ^{63}Ni in dilute acid solution leads to 3 to 6 percent absorption of the radio-labeled nickel regardless of the dosing level. A more systematic and directly relevant study concerning nickel bioavailability in human diets is that of Solomons and co-workers (1982), who showed bioavailability of nickel to be quite dependent on dietary composition. Adult human volunteers ingested 5.0 mg of nickel as the soluble sulfate in water and the resulting serum nickel profiles were compared to those obtained when the same amount of nickel was given in beverages and two test meals, including an average American breakfast. All beverages except soft drink suppressed nickel absorption, as did the two test diets. When the chelating agent, EDTA, was added to the diet, nickel in serum was suppressed to a point below even fasting baseline levels.

4.1.3 Percutaneous Absorption of Nickel

Percutaneous absorption of nickel is mainly considered to be important in the dermatopathologic effects of this agent, such as contact dermatitis, and such absorption is restricted to the passage of nickel past the outermost layers of skin deep enough to bind with apoantigenic factors.

Wells (1956) demonstrated that divalent nickel penetrates the skin at sweat-duct and hair-follicle ostia and binds to keratin. Using cadaver skin, Kolpakov (1963) found that nickel II accumulated in the Malpighian layer, sweat glands, and walls of blood vessels. Spruit et al. (1965) have shown that nickel penetrates to the dermis.

Values for the amounts of nickel passing through outer layers of skin relative to amounts applied have not been determined. Samitz and Pomerantz (1958) reported that the relative extent of nickel penetration is enhanced by sweat and detergents.

Mathur and co-workers (1977) reported the systemic absorption of nickel from the skin using nickel sulfate at very high application rates. After 30 days of exposure to nickel at doses of 60 and 100 mg Ni/kg, a number of testicular lesions were observed in rats, while hepatic effects were seen after 15 days at these exposure levels. It is not possible to calculate any absorption data from this study.

4.1.4 Transplacental Transfer of Nickel

Evidence for the transplacental transfer of nickel to the fetus dates to the study of Phatak and Patwardhan (1950), who found that newborn of rats fed nickel in various chemical forms had whole-body levels of 22 to 30 ppm when the mothers received 1000 ppm nickel in the diet.

Pregnant mice given nickel chloride intraperitoneally as one dose (3.5 mg/kg) at 16 days of gestation showed transfer to placental tissue with peak accumulation having occurred by eight hours postexposure (Lu et al., 1976).

Jacobsen et al. (1978), using ^{63}Ni-labeled nickel chloride and single intraperitoneal injections into pregnant mice at day 18 of gestation, showed rapid passage from mother to fetus, with fetal tissues generally showing higher concentrations than that of the mothers. Within the fetus, the highest nickel levels were seen in the kidney, and the lowest levels were recorded in the brain. Furthermore, Olsen and Jonsen (1979) used ^{63}Ni whole body radiography in mice to determine that placental transfer occurs throughout gestation.

A similar study is that of Sunderman et al. (1978), who administered ^{63}Ni-labeled solution to pregnant rats intramuscularly. Embryo and embryonic membrane showed measurable label by day eight of gestation, while autoradiograms demonstrated label in yolk sacs of placentae one day postinjection (day 18 of gestation).

Several reports indicate transplacental passage of nickel also occurs in man. Stack et al. (1976) showed levels of 11 to 19 ppm in dentition from four fetuses as well as a mean element concentration of 23 ppm in teeth from 25 cases of stillbirths and neonatal deaths.

Casey and Robinson (1978) found detectable levels of nickel in tissue samples from 40 fetuses of 22 to 43 weeks gestation, with levels in liver, heart, and muscle being comparable to those seen in adult humans. Values ranged from 0.04 to 2.8 ppm (µg Ni/g dry weight). This study suggests ready movement of nickel into fetal tissues, given the similarity in fetal versus adult human levels.

Creason et al. (1976) studied the maternal-fetal tissue levels of 16 trace elements in eight selected U.S. communities. The authors reported geometric mean nickel levels of 3.8 µg/100 ml in maternal blood, 4.5 µg/100 ml in cord blood, and 2.2 µg/100 g in placenta. In order to examine the relative levels of maternal and cord blood trace elements, ratios of these values were computed and a standard t-test was applied to the logs of these ratios. The geometric mean of the ratio for nickel was 1.15 based upon 166 observations. This ratio was not significantly different from 1 at the .05 level. While statistical significance was not shown, this study, nevertheless, indicated possible transplacental passage of nickel in humans.

4.2 TRANSPORT AND DEPOSITION OF NICKEL IN MAN AND EXPERIMENTAL ANIMALS

The kinetic processes governing the transport and distribution of nickel in various organisms are dependent upon the modes of absorption, the rate and level of nickel exposure, the chemical form of nickel, and the physiological status of the organism.

4.2.1 Nickel in Blood

Blood is the main route by which absorbed nickel is delivered to other tissues. While it is difficult to determine from the literature the exact partitioning of nickel between erythrocytes and plasma or serum for unexposed individuals, serum levels are useful indicators of blood burden and, to a more limited extent, exposure status (National Academy of Sciences, 1975). Regarding the latter, it is important here to note that serum nickel would not reflect amounts of insoluble and unabsorbed nickel deposited in lungs. In unexposed individuals, serum nickel values are approximately 0.2 to 0.3 μg/dl.

The study of Christensen and Lagesson (1981) is particularly helpful in addressing the issue of nickel partitioning between plasma and erythrocytes in human subjects. Baseline serum and whole blood nickel values, as well as changes in these media over time, were measured in adult human volunteers (N = 8) ingesting a single quantity of 5.6 mg nickel. Mean baseline values for serum and whole blood were 1.6 and 3.0 μg/l, respectively, with large variance, indicating that under steady-state conditions of low nickel absorption there is no statistically significant enrichment in either fraction and that it is difficult to obtain any correlation. Analytical variance in baseline values is often due to contamination. Partitioning of nickel into the two fractions was not significantly different after ingestion of the nickel salt. Furthermore, nickel levels in serum and whole blood, being much higher after ingestion of the nickel, were strongly correlated ($r = 0.99$, $p < 0.001$) over the entire study period.

The kinetics of nickel removal from serum in these same subjects showed a single elimination half-time of 11 hours over the 51-hour study period. Whether the serum half-time in humans is dose dependent cannot be determined. In a study of nickel-exposed workers, Tossavainen and co-workers (1980) used a linear one-compartment kinetic modeling approach to estimate that the half-time of nickel in plasma of four electroplaters ranged from 20 to 34 hours.

The results of Onkelinx et al. (1973) indicate that the kinetics of nickel elimination from plasma or serum in experimental animals are characterized by a two-compartment distribution, with corresponding half-times which can be calculated at several hours and several days, respectively.

Distribution of serum-borne nickel among the various biomolecular components has been discussed in some detail in recent reviews (National Academy of Sciences, 1975; Mushak, 1984), and it will mainly be noted here that serum albumin is the main carrier protein in sera of man, rabbit, rat, and bovine. Furthermore, there exists in sera of man and rabbits a nickel-rich metalloprotein identified as an α_1-macroglobulin (nickeloplasmin) in rabbits and as a 9.5 S α_1-glycoprotein in man. Sunderman (1977) has suggested that nickeloplasmin may be a complex of the α_1-glycoprotein with serum α_1-macroglobulin.

In vitro study of nickel II binding in human serum (Lucassen and Sarkar, 1979) shows histidine to be a major micromolecular binding species and an equilibrium between albumin and histidine may be an important factor in the transfer of nickel from blood to other tissues.

Glennon and Sarkar (1982) studied, in some detail, the binding of nickel II to human serum albumin (HSA) and found, using equilibrium dialysis of HSA, that: (1) both nickel and copper bind HSA at the same site; (2) the binding site involves the a-amino group of aspartate, two deprotonated peptide-N groups, the imidazole N atom of histidine, and the carboxyl of aspartate; and (3) a ternary complex of histidine, HSA, and nickel exists under equilibrium conditions, suggesting that nickel transfer from HSA to histidine may facilitate the movement of nickel from the serum into other tissues. Using nuclear magnetic resonance techniques, Laussac and Sarkar (1984) confirmed that nickel binding in human serum albumin takes place at peptide 1-24, the N-terminal tripeptide segment containing alanine, histidine, and aspartate.

Using two-dimensional immunoelectrophoretic techniques and autoradiography, Scott and Bradwell (1984) determined that radio-labeled nickel in human serum was bound mainly to two proteins: albumin and an alpha-2-protein, possibly nickeloplasmin. The relative *in vitro* partitioning of the metal between the two proteins was approximately 2 to 1, respectively. The relative high amount of nickel in the human alpha-2-protein may indicate a more important role of this protein in nickel homeostasis than had been previously assumed.

While the relative amounts of protein-bound nickel in sera of various species have a considerable range (Hendel and Sunderman, 1972) which may reflect relative binding strengths of albumins, the total nickel levels are markedly similar, as may be seen in Table 4-1.

4.2.2 Tissue Distribution of Nickel

4.2.2.1 Human Studies. The distribution of nickel in tissues of human populations has been reviewed by Mushak (1984).

Generally, nickel content in human tissue has been studied through autopsy specimens. The problems attending the use of such specimens determine the reliability of such measures. Furthermore, it appears that earlier data are subject to questionable analytical reliability and sensitivity.

The studies of Schroeder and Tipton and co-workers (Schroeder et al., 1962; Tipton and Cook, 1963; Tipton et al., 1965) indicate that many autopsy tissues

TABLE 4-1. SERUM NICKEL IN HEALTHY ADULTS OF SEVERAL SPECIES

Species (N)	Nickel concentration, μg/l[a]
Domestic horse (4)	2.0 (1.3-2.5)
Man (47)	2.6 (1.1-4.6)
Jersey cattle (4)	2.6 (1.7-4.4)
Beagle dog (4)	2.7 (1.8-4.2)
Fischer rat (11)	2.7 (0.9-4.1)
British goat (3)	3.5 (2.7-4.4)
New Hampshire chicken (4)	3.6 (3.3-3.8)
Domestic cat (3)	3.7 (1.5-6.4)
Guinea pig (3)	4.1 (2.4-7.1)
Syrian hamster (3)	5.0 (4.2-5.6)
Yorkshire pig (7)	5.3 (3.5-8.3)
New Zealand rabbit (24)	9.3 (6.5-14.0)
Maine lobster (4)	12.4 (8.3-20.1)

[a] Mean (and range)

Source: Sunderman et al. (1972).

evaluated in the respective laboratories of these workers were below the detection limits available at that time. Therefore, information on relative nickel content could only be gained by examining the relative frequency of nickel detection across tissues. By using this method, these workers noted a greater uptake of nickel in lung, kidney, liver, heart, trachea, aorta, spleen, skin, and intestine. Overall, levels adjusted to wet weight indicated less than 0.05 μg/g in most cases. Higher levels in skin, intestine, and lung reflected some fraction of the unabsorbed element. Of importance to nickel pharmacokinetics was the demonstration by these workers that the accumulation of the element does not increase with increasing age except in the lung. Lung accumulation reflects the deposition of insoluble nickel particulates. Other studies support the observation of nickel accumulation in lung. Sunderman et al. (1971) reported that lung from accidental death victims had the highest levels (0.016 μg Ni/g wet weight) of all tissues. Andersen and Hogetveit (1984) found that autopsied lung samples from former nickel refinery workers in Norway have nickel contents ranging from 2 to 1350 μg/g, depending on worksite classification within a nickel operation.

Bernstein and co-workers (1974) reported that mean nickel content of lung and lymph node samples from the autopsies of 25 New York City residents were

0.23 and 0.81 μg Ni/g wet weight, respectively. The relatively high values in lymph nodes indicated that lymphatic clearance of particulate nickel lodged in lung also occurs in humans, such clearance being demonstrated in experimental animals (vide supra).

Sumino et al. (1975) analyzed nickel in autopsy samples from 30 non-exposed Japanese and also found highest levels in lung (0.16 μg/g wet weight), followed by liver (0.08) and kidney (0.1 μg/g wet weight).

Various studies of individuals accidentally exposed to nickel carbonyl have indicated that lung has the highest uptake, followed by kidney, liver, and brain (National Academy of Sciences, 1975). The carbonyl differs from other forms of nickel in its penetration of the blood-brain barrier, as evidenced by brain nickel content.

Age-dependent accumulation of nickel in tissues appears to occur only in the lung, other soft tissues showing no accumulation. Such accumulation may be associated with highly insoluble forms of inhaled nickel. The question of accumulation in mineralizing tissue has been addressed in several reports. Knuuttila et al. (1982) studied the content of nickel, along with other elements, in human cancellous bone in 88 subjects having normal mineral status. The authors found a mean concentration (± 1 S.D.) of 1.29 (± 0.83) μg/Ni/g. Bone nickel did not vary with age. Lappalainen and Knuuttila (1981) observed no accumulation in dentition with age. Extracted permanent teeth were obtained from 89 subjects, 8 to 67 years of age. Mean nickel levels were higher in enamel (43.8 mg/g) than in dentine (31.4 μg/g).

4.2.2.2 Animal Studies. A number of studies of the distribution of nickel in experimental animals exposed to nickel carbonyl have been described (National Academy of Sciences, 1975).

Armit (1908) exposed dogs, cats, and rabbits to nickel carbonyl vapor and was able to measure elevated nickel levels in lung, brain, kidney, and adrenal glands. Later investigators observed elevated, rapidly eliminated levels of nickel in lungs, brain, kidney, and liver of various animal species (Mikheyev, 1971; Sunderman and Selin, 1968; Ghiringhelli and Agamennone, 1957; Sunderman et al., 1957; Barnes and Denz, 1951).

Sunderman and Selin (1968) have shown that one day after exposure to inhaled ^{63}Ni-labeled nickel carbonyl, viscera contained about half of the total absorbed label with one-third in muscle and fat. Bone and connective tissue accounted for about one-sixth of the total. Spleen and pancreas also appear to take up an appreciable amount of nickel. Nickel carbonyl has also been shown to be excreted in breath following its intravenous administration in rats (Kasprzak and Sunderman, 1969; Sunderman et al., 1968; Sunderman and Selin, 1968). Presumably, nickel carbonyl crosses the alveolar membrane intact from either route, inhalation or injection, suggesting that its stability is greater than has usually been assumed. Retained nickel carbonyl appears to undergo decomposition to carbon monoxide and possibly zero-valent nickel in erythrocytes and other tissues, followed by intracellular oxidation of the element to the divalent form and subsequent release into serum (National Academy of Sciences, 1975).

A number of reports in the literature describe the tissue distribution of divalent nickel following parenteral administration of nickel salts. These studies have been of two types: tissue nickel content assessment or studies measuring the kinetics of nickel deposition and clearance within a modeling framework. These data are summarized in Table 4-2.

It can be generally stated that nickel administered this way leads to highest accumulation in kidney, endocrine glands, lung, and liver. Relatively little nickel is lodged in neural tissue, consistent with the observed low neurotoxic potential of divalent nickel salts. Similarly, there is relatively slight uptake into bone, consistent with other evidence that nickel is rather rapidly and extensively cleared from organisms, with little retention in soft or mineral tissue.

Sunderman and Fraser (1983) examined the ability of soluble nickel ($NiCl_2$) to induce the metal binding protein, metallothionein (MT), in livers and kidneys of Fischer rats. Nickel II was moderately active as an inducer at dosing levels of 6.3 and 47 mg/kg (i.p.), being more effective for hepatic MT. Since actinomycin did not prevent MT induction, the mechanism for nickel induction of MT is apparently unrelated to enhanced copper/zinc uptake. However, nickel may induce MT synthesis through either hormonal disturbances or stimulated translation of mRNA in liver and kidney ribosomes.

Absorption and tissue distribution of nickel in animals orally exposed appear to be dependent upon the relative amounts of the agent employed. Schroeder et al. (1974) could find no uptake of nickel in rats chronically exposed to nickel in drinking water (5 μg/ml) over the lifetime of the animals. Phatak and Patwardhan (1950) reported the effects on tissue accumulation of different nickel compounds given orally to rats. Among the three chemical forms of nickel used, i.e., carbonate, nickel soaps, and metallic nickel catalyst, tissue levels

TABLE 4-2. TISSUE DISTRIBUTION OF NICKEL II AFTER PARENTERAL ADMINISTRATION

Species	N	Dosage[a]	Relative distribution of ^{63}Ni	Reference
Mouse	8	6.2 mg/kg (one intraperitoneal injection)	Kidney > lung > plasma > liver > erythrocyte > spleen > bladder > heart > brain > carcass (muscle, bone, and fat)	Wase et al. (1954)
Rat	4	617 µg/kg (one intravenous injection)	Kidney > lung > adrenal > ovary > heart > gastrointestinal tract > skin > eye > pancreas > spleen = liver > muscle > teeth > bone > brain = fat	Smith and Hackley (1968)
Guinea pig	6	1 mg/kg (subcutaneously for 5 days)	Kidney > pituitary > lung > liver > spleen > heart > adrenal > testis > pancreas > medulla oblongata = cerebrum = cerebellum	Clary (1975)
Rabbit	3	240 µg/kg (one intravenous injection)	Kidney > pituitary > serum > whole blood > skin > lung > heart > testis > pancreas > adrenal > duodenum > bone > spleen > liver > muscle > spinal cord > cerebellum > medulla oblongata = hypothalamus	Parker and Sunderman (1974)
Rabbit	4	4.5 µg/kg (intravenously for 34-38 days)[b]	Kidney > pituitary > spleen > lung > skin > testis > serum = pancreas = adrenal > sclerae > duodenum = liver > whole blood > heart > bone > iris > muscle > cornea = cerebellum = hypothalamus > medulla oblongata > spinal cord > retina > lens > vitreous humor	Parker and Sunderman (1974)
Mouse	12	4.6 µg/kg (10-20 µCi^{63}Ni given intravenously in one dose)[c]	Kidney > lung > sternal cartilage > pancreas	Oskarsson and Tjalve (1979)

[a] Unless otherwise noted, animals were killed 2 hours after the last injection of $^{63}NiCl_2$.

[b] Animals were killed 24 hours after the last injection of $^{63}NiCl_2$.

[c] Three animals were killed 1 hour, 24 hours, 5 days and 10 days, respectively, after the last injection of $^{63}NiCl_2$.

Source: Adapted from National Academy of Sciences (1975) except for Oskarsson and Tjalve (1979).

were greatest in the groups fed the carbonate. O'Dell and co-workers (1971) fed calves supplemental nickel in the diet at levels of 62.5, 250, and 1000 µg/g. While levels of nickel were somewhat elevated in pancreas, testis, and bone at 250 µg/g, pronounced increases in these tissues were seen at 1000 µg/g. Whanger (1973) exposed weanling rats to nickel (acetate) in the diet at levels up to 1000 µg/g. As nickel exposure was increased, nickel content of kidney, liver, heart, and testis was also elevated, with greatest accumulation in the kidneys. Spears et al. (1978) observed that lambs given tracer levels of ^{63}Ni orally with or without supplemental nickel in diet had the highest levels of the label in kidney; the relative levels in kidney, lung, and liver being less for the low-nickel group.

Comparison of the above studies suggests that a homeostatic mechanism exists to regulate low levels of nickel absorption, e.g., 5 µg/g, but such regulation is overwhelmed in the face of large levels of nickel challenge.

4.2.3 Subcellular Distribution of Nickel

Nickel toxicity to organelles is associated with specific patterns of subcellular distribution, particularly with respect to carcinogenicity.

Earlier studies suggest that: (1) 70 to 90 percent of cellular nickel is lodged in the nucleus in rhabdomyosarcoma induced by nickel subsulfide (Webb et al., 1972) and is distributed between nucleolus and sap + chromatin fractions; (2) nuclear binding involves both RNA and DNA (Heath and Webb, 1967); (3) similar nuclear accumulation is obtained with intrarenal administration of the subsulfide in rats (Jasmin and Riopelle, 1976); and (4) lung and liver of rats exposed to nickel carbonyl exhibit highest nickel accumulation in microsomal and supernatant fractions (Sunderman and Sunderman, 1963).

The binding of nickel to chromatin, nuclei, and nuclear proteins was studied by Ciccarelli and Wetterhahn (1984) in rats given nickel carbonate (40 mg/kg, i.p., single dose). The relative amount of nickel bound to whole chromatin was greater for kidney than for liver and was directly related to nuclear nickel content. In addition, much higher levels of nickel were found in the DNA-histone complex from kidney as compared to liver. Other binding sites where significant nickel levels were found included non-histone proteins from both kidney and liver nuclei and histone octamer proteins from kidney.

A number of recent studies indicate that subcellular partitioning of nickel *in vivo* or *in vitro* is markedly different between insoluble nickel compounds and soluble nickel salts. Herlant-Peers et al. (1983) reported that intraperitoneal injection of ^{63}Ni-labeled nickel chloride solution into mice was associated with a pattern of label incorporation into subcellular fractions over short time periods. This pattern was characterized by generally lower accumulation in nuclei than in cytosol, mitochondria, or microsomes.

In vitro cell studies of Costa et al. (1981) indicate that carcinogenic nickel subsulfide, crystalline nickel sulfide, and crystalline nickel subselenide are all actively phagocytized and enter Syrian hamster embryo or Chinese hamster ovary cells with subsequent transfer of nickel to cell nuclei. Harnett et al. (1982) compared the differential binding of labeled nickel as the insoluble crystalline nickel sulfide and soluble nickel chloride solution in cultured Chinese hamster ovary cells. RNA and DNA binding of nickel following sulfide exposure was 300 to 2000 times greater than with the soluble divalent nickel. In describing the possible mechanistic basis for selective uptake of nickel by nuclei from phagocytized insoluble nickel particles, consideration should be given to the observation that some process, possibly endocytosis, delivers the particles adjacent to the nucleus, as determined by ultrastructural observation. Eventual dissolution would likely permit nickel ion uptake by the nuclear membrane.

As noted above, administration of soluble or volatile nickel to animals shows a sizable fraction remaining in cell supernatant. Sunderman et al. (1981) characterized the biomolecular distribution of nickel in renal cytosol in rats given injected nickel II. The greatest fraction, approximately 68 percent, was bound to low-weight components, less than 2000 daltons. The remainder was partitioned among molecules of 10,000 to less than 130,000 molecular weight, with molecules in the higher weight range comprising the most prominent portion of this fraction. This pattern was confirmed in a later study using high-performance size-exclusion chromatography (Sunderman et al., 1983). Abdulwajid and Sarkar (1983), on the other hand, have claimed that their method of purification of renal cytosolic binding proteins results in most of the nickel being bound to a glycoprotein (derived from renal basement protein) of 15,000 to 16,000 molecular weight.

4.3 RETENTION AND EXCRETION OF NICKEL IN MAN AND ANIMALS

When studying the systemic retention of an element such as nickel, it is necessary to differentiate between relatively short-term retention associated with replacement in tissue of optimal levels of an essential element (see Chapter 9) versus accumulation with organism age, such as is exhibited with lead in mineralizing tissue or cadmium in kidney cortex.

The ICRP (International Commission on Radiological Protection, 1981) has estimated that the human adult body contains about 10 mg nickel for unexposed subjects. The ICRP has also estimated an elimination half-time of 1200 days (approximately 3.3 years) based upon a daily net retention of around 30 percent of the amount absorbed from a rather high daily ingestion of 400 µg nickel. Bennett (1982), however, reported a body burden of 500 µg nickel, many-fold lower than the ICRP values, based upon calculations of a body nickel retention time (not half-time) of 200 days under steady-state conditions of exposure. Bennett's figure is an estimate from average nickel levels of 7 ng/g tissue.

The data for teeth and bone nickel levels described above (1.3 µg/g bone, 30 to 40 µg/g dentition) lead to a body nickel burden closer to the ICRP estimate. If it is assumed that the current daily nickel intake is closer to 200 µg (Myron et al., 1978; Clemente et al., 1980) than the ICRP value of 400 µg, then the biological half-time is increased, being entirely determined by mineral tissue burden. Since nickel in bone is relatively constant with age, it presumably is constantly being resorbed and deposited in the mineral matrix. The daily net retention figure of 30 percent for absorbed nickel, as estimated by the ICRP for normal human intake, may or may not apply to excessive intake.

The excretory routes for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake. Unabsorbed dietary nickel is simply lost in the feces. Given the relatively low extent of gastrointestinal absorption (vide supra), fecal levels of nickel roughly approximate daily dietary intake of 300 to 500 µg/day in man.

Urinary excretion in man and animals is usually the major excretory route for absorbed nickel. Reported normal levels in urine vary considerably in the literature, and earlier value variance probably reflects both methodological limitations as well as inherent biological variation. More recent studies suggest values of 2 to 4 µg/l (Andersen et al., 1978; McNeely et al., 1972).

Biliary excretion is also a possible clearance route for absorbed nickel and is known to occur in the rat (Smith and Hackley, 1968), the calf (O'Dell et al., 1971), and the rabbit (Onkelinx et al., 1973). However, Marzouk and Sunderman (1985), employing relatively accurate methodology, observed that biliary excretion of nickel in the rat, when administered in single subcutaneous doses, only amounted to approximately 0.3 percent of the total dose over a 24-hour period, thereby constituting a rather minor route for excretion. Whether biliary excretion occurs in man is unknown.

Sweat can constitute a major route of nickel excretion. Hohnadel and co-workers (1973) determined nickel levels in the sweat of healthy subjects sauna bathing for brief periods at 93°C to be 52 ± 36 μg/l for men and 131 ± 65 μg/l for women.

The role of nickel deposition in hair as an excretory mechanism in man has prompted a number of studies. The use of hair nickel levels in assessing overall nickel body burdens remains to be widely accepted. Schroeder and Nason (1969) have reported sex-related differences in nickel levels of human hair samples, female subjects having nickel levels (3.96 μg/g, S.E.M. = ± 1.06) about fourfold those of men (0.97 μg/g, S.E.M. = ± 0.15). Such a difference, however, was not encountered by Nechay and Sunderman (1973) nor were their average sample values as high. The differences in these two studies serve to point out some of the difficulties in establishing quantitative relationships for the role of hair levels in nickel metabolism.

Several studies have demonstrated that excretion of nickel in human milk is quite low and should be considered a minor route of excretion in lactating women (Feeley et al. 1983; Mingorance and Lachica, 1985).

In experimental animals, urinary excretion is the main excretion route for nickel compounds introduced parenterally. Onkelinx et al. (1973) studied the kinetics of injected ^{63}Ni metabolism in rats and rabbits. In both species, a two-compartment model of excretion could be discerned, consisting of fast and slow components. In the rabbit, better than 75 percent of the dose was excreted within 24 hours, while comparable excretion in the rat required 3 days. In a later study, Onkelinx (1977) reported whole body kinetics of ^{63}Ni in rats. The time course of plasma nickel levels entailed first-order kinetics analyzable in terms of a two-compartment model. The major portion of nickel elimination was accounted for by renal excretion.

Chausmer (1976) has measured exchangeable nickel in the rat using ^{63}Ni given intravenously. Tissue exchangeable pools were directly estimated and compartmental analysis performed by computer evaluation of the relative isotope retention versus time. Within 16 hours, the kidney had the largest labile pool with two intracellular compartments. Liver, lung, and spleen pools could also be characterized by two compartments, while bone fit a one-compartment model.

Corresponding half-times for the fast and slow components were several hours and several days, respectively.

Animals exposed to nickel carbonyl via inhalation exhale a part of the respiratory burden of this agent within 2 to 4 hours, while the balance is slowly degraded _in vivo_ to divalent nickel and carbon monoxide with nickel eventually undergoing urinary excretion (Mikheyev, 1971; Sunderman and Selin, 1968).

The time course of labeled-nickel urinary excretion in rats given a single injection (4 mg/kg, 12.5 μ Ci^{63}Ni/mg cold Ni, as chloride) was studied by Verma et al. (1980) who reported nickel to be excreted as a mixture of complexes within 24 hours of dosing, the binding species having a molecular weight of 200 to 250.

4.4 FACTORS AFFECTING NICKEL METABOLISM

A number of disease states and other physiological stresses are reported to alter the movement and tissue distribution of nickel in man as well as experimental animals. Furthermore, _in vivo_ movement of nickel may be deliberately altered to enhance nickel removal from the organism to minimize toxicity in cases of excessive exposure, specifically via the use of nickel chelating agents in the clinical management of nickel poisoning.

In man, increased levels of serum nickel are seen in cases of acute myocardial infarction (AMI) (Sunderman et al., 1972; McNeely et al., 1971; D'Alonzo and Pell, 1963), such alterations presently being considered as secondary to leukocytosis and leukocytolysis (Sunderman, 1977). Leach et al. (1985) compared the serum nickel levels of healthy adults (N = 33) with patients having acute myocardial infarction (AMI, N = 37) and with patients having unstable angina pectoris (N = 24). Patients were monitored periodically after hospitalization, every eight hours on day one and daily for the second and third days. Hypernickelemia was seen in 65 percent of those patients with AMI and in 54 percent of those with unstable angina pectoris. There was no relationship of serum nickel level to age, sex, medication, or cigarette smoking. The authors concluded that elevated nickel may be associated with the pathogenesis of ischemic myocardial injury.

Serum nickel levels are also elevated in acute stroke and extensive burn injury (McNeely et al., 1971), while reduction is seen in hepatic cirrhosis or uremia, possibly secondary to hypoalbuminemia.

Rubányi et al. (1983) have claimed a role for endogenous nickel release in the myocardial injury and vasoconstriction attending acute burn injury in rats. Thermal burn injury in rats was seen to induce a rise up to fivefold ($p < 0.001$) in serum nickel. Nickel ion was seen to be released directly from myocardial cells by cytochemical techniques. Nickel sensitivity of coronary vessels in perfused hearts from burn-injured rats, measured in terms of total coronary resistance, was also significantly enhanced. One difficulty with this report lies in the serum nickel value reported for the control group. At 100 µg/l, this value is approximately 50-fold over levels generally observed. While the control value indicates a large systematic contamination error, the relative and huge fivefold increase to 500 µg/l in the test group is inexplicable.

Several recent studies demonstrate an association of serum nickel with chronic renal failure and hemodialysis. According to Drazniowsky and co-workers (1985), serum nickel levels were elevated in hemodialysis patients (N = 16, median 7.6 µg/l, $p < 0.01$) compared to normal subjects (N = 71, median 1.0 µg/l). Similarly, Savory et al. (1985) have observed that nickel in serum (3.7 versus 0.4 µg/l) is significantly elevated ($p < 0.00005$) in hemodialysis patients. Hopfer et al. (1985) have determined that the hemodialysis hypernickelemia seen by them and other researchers (vide supra) is based on nickel-contaminated dialysis solution. As evidence, the authors note that reduction of solution nickel by about 30 percent results in a concomitant decrease of the same amount in serum nickel of dialysis subjects.

Palo and Savolainen (1973) reported that hepatic nickel was increased tenfold over normal values in a deceased patient with aspartylglycosaminuria, a metabolic disorder characterized by reduced activity of aspartyl-β-glucosaminidase.

Other stresses appear to have an effect on nickel metabolism. Significant reduction in serum nickel has been seen in mill workers exposed to extremes of heat (Szadkowski et al., 1970), probably due to excessive nickel loss through sweating, as was noted earlier.

Tissue nickel levels have been reported to be elevated in rats during pregnancy (Spoerl and Kirchgessner, 1977). In a study on humans, Rubányi et al. (1982) showed a 60 percent decrease in serum nickel in pregnant women, which rose to normal at parturition, and a 20-fold, transitory rise in serum nickel at 5 minutes postparturition. By 60 minutes, serum values were normal. Unfortunately, several problems have been noted with this study including the reliability of the analytical methods employed and the inability of others to replicate the results (Nomoto et al., 1983).

Use of various classes of chelating agents employed to expedite the removal of nickel from man and animals has been reported. The data have been reviewed elsewhere (Sunderman, 1977; National Academy of Sciences, 1975), and will only be summarized in this section.

On the basis of reported clinical experience, sodium diethyldithiocarbamate (dithiocarb) is presently the drug of choice in the management of nickel carbonyl poisoning, being preferable overall to EDTA salts, 2, 3-dimercaptopropanol (BAL), and penicillamine. While it has been assumed that such agents work to accelerate the urinary excretion of absorbed amounts of nickel before extensive tissue injury can result, recent evidence from experimental animals suggests that the dithiocarbamates may serve to markedly alter the distribution of nickel as well as its retention _in vivo_ (Oskarsson and Tjälve, 1980). Similar results have been reported using alkyl thiuram sulfides, agents which readily undergo _in vivo_ reduction to the dithiocarbamates (Jasim and Tjälve, 1984). The chemotherapeutic function of the dithiocarbamates in nickel intoxication, therefore, may be to divert nickel II from sensitive physiological binding sites via formation of inert, lipophilic complexes, rather than to enhance the lowering of body nickel burdens.

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5. NICKEL TOXICOLOGY

Both acute and chronic effects of exposure to various nickel compounds have been extensively documented over the years. The following chapter discusses these non-mutagenic/carcinogenic effects of exposure to various nickel compounds. Because of the large volume of information available regarding the mutagenic and carcinogenic effects, as well as the reproductive effects of nickel exposure, these topics have been discussed in following chapters.

5.1 ACUTE EFFECTS OF NICKEL EXPOSURE IN HUMANS AND ANIMALS

5.1.1 Human Studies

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl, $Ni(CO)_4$, a volatile, colorless liquid formed when finely divided nickel comes into contact with carbon monoxide, as in the Mond process for purification of nickel (Mond et al., 1890). A sizable body of literature has developed over the years dealing with the acute inhalation exposure of nickel-processing workers to nickel carbonyl (Sunderman, 1977; National Institute for Occupational Safety and Health, 1977; National Academy of Sciences, 1975). Since much of this information is relevant mainly to industrial accidents and occupational medicine rather than general environmental health, it is not appropriate to accord it detailed discussion in this document.

According to Sunderman (1970) and Vuopala et al. (1970), who have studied the clinical course of acute nickel carbonyl poisoning in workmen, clinical manifestations include both immediate and delayed symptomatology. In the former, frontal headache, vertigo, nausea, vomiting, insomnia, and irritability are commonly seen, followed by an asymptomatic interval before the onset of insidious, more persistent symptoms. These include constrictive chest pains, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Aside from the weakness and hyperpnea, the symptomatology strongly resembles that of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in humans and animals. Pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage and edema accompanied by derangement of alveolar cells, degeneration of bronchial epithelium, and formation of fibrinous intra-alveolar exudate. Roentgenological follow-up on patients surviving acute episodes of exposure frequently indicates pulmonary fibrosis.

In humans, nephrotoxic effects of nickel have been clinically detected in some cases of accidental industrial exposure to nickel carbonyl (Carmichael, 1953; Brandes, 1934). This takes the form of renal edema with hyperemia and parenchymatous degeneration.

5.1.2 Animal Studies

The pronounced pulmonary tract lesion formation seen in animals acutely exposed to nickel carbonyl vapor strongly overlaps that reported for cases of acute industrial poisoning (Armit, 1908; Barnes and Denz, 1951; Kincaid et al., 1953; Sunderman et al., 1961; Hackett and Sunderman, 1967, 1969). The lung is the target organ for effects of nickel carbonyl in animals regardless of the route of administration. The response of pulmonary tissue is very rapid, interstitial edema developing within one hour of exposure. There is subsequent proliferation and hyperplasia of bronchial epithelium and alveolar lining cells. By several days postexposure, severe intra-alveolar edema with focal hemorrhage and alveolar cell degeneration has occurred. In animals that do not survive acute exposures, death usually occurs by the fifth day. Animals surviving the acute responses show regression of cytological changes with fibroblastic proliferation within alveolar interstitium.

Acute renal injury with proteinuria and hyaline casts were observed by Azary (1879) in cats and dogs given nickel nitrate. Pathological lesions of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl (Hackett and Sunderman, 1967; Sunderman et al., 1961; Kincaid et al., 1953). Gitlitz et al. (1975) observed aminoaciduria and proteinuria in rats after single intraperitoneal injection of nickel chloride, the extent of the renal dysfunction being dose-dependent. Proteinuria was observed at a dose of 2 mg/kg, while higher dosing occasioned aminoaciduria. Ultrastructurally, the site of the effect within the kidney appears to be glomerular epithelium. These renal effects were seen to be transitory, abating by the fifth day.

5.2 CHRONIC EFFECTS OF NICKEL EXPOSURE IN HUMANS AND ANIMALS

5.2.1 Nickel Allergenicity

Nickel dermatitis and other dermatological effects of nickel have been documented in both nickel worker populations and populations at large (National Academy of Sciences, 1975). Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological picture of nickel sensitivity offers proof that it may be more of a problem in individuals not having occupational exposure to nickel but encountering an increasing number of nickel-containing commodities in their everyday environment.

5.2.1.1 Clinical Aspects of Nickel Hypersensitivity. Occupational sources of nickel that have been associated with nickel sensitivity include mining, extraction, and refining of the element as well as such operations as plating, casting, grinding, polishing, and preparation of nickel alloys (National Academy of Sciences, 1975). Although the frequency of nickel dermatitis has considerably abated owing to advances in both control technology and industrial medicine, it may still persist in electroplating shops (National Academy of Sciences, 1975).

Nonoccupational exposure to nickel potentially leading to dermatitis includes nickel-containing jewelry, coinage, tools, cooking utensils, stainless steel kitchens, prostheses, and clothing fasteners. Women appear to be particularly at risk for dermatitis of the hands and their continuous contact with many of the nickel-containing commodities noted above has been implicated by Malten and Spruit (1969) as a factor in dermatitis.

Nickel dermatitis usually begins as itching or burning papular erythema in the web of fingers and spreads to the fingers, wrists, and forearms. Clinically, the condition is usually manifested as a papular or papulovesicular dermatitis with a tendency toward lichenification, having the characteristics of atopic, rather than eczematous, dermatitis.

According to Calnan (1956), on the basis of a large number of cases, nickel dermatitis has a unique topographical distribution pattern: (1) primary: areas in direct contact with the element; (2) secondary: spreading of the dermatitis in a symmetrical fashion; and (3) associated: afflicted areas having no relation to contact areas. Furthermore, the affliction may persist some time after removal of obvious sources of exposure.

A clear relationship between atopic dermatitis and that elicited by nickel has been precluded by conflicting reports in the literature. Watt and Baumann (1968) showed that atopy was present in 15 of 17 young patients with earlobe nickel dermatitis, but other workers (Caron, 1964; Marcussen, 1957; Calnan, 1956; Wilson, 1956) have failed to demonstrate any connection between the two disorders. Juhlin et al. (1969) demonstrated elevated immunoglobulin (IgE) levels in atopy patients, while Wahlberg and Skog (1971) saw no significant increases of IgE in patients having nickel and atopic dermatitis histories.

The occurrence of pustular patch test reactions to nickel sulfate has been considered significant in connecting nickel and atopic dermatitis (Becker and O'Brien, 1959). Uehara et al. (1975) reported that pustular patch test reactions to five percent nickel sulfate were regularly produced in patients with atopic dermatitis, but only when applied to areas of papulae, erythema, lichenification, and minimal trauma; such response seldom occurred on normal-appearing skin surface. Furthermore, traumatizing the test areas in control, as well as dermatitic subjects, furnished positive responses. These authors suggest that pustular patch testing is primarily a primary irritant reaction.

Christensen and Möller (1975a) found that of 66 female patients with hand eczema and nickel allergy, 51 had an eczema of the pompholyx type, i.e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers. Of these, 41 had pompholyx only, while the remainder had at least one of the following additional diagnoses: allergic contact eczema, irritant dermatitis, nummular eczema, or atopic dermatitis. These workers also found that the condition was not influenced by any steps taken to minimize external exposure. Subsequently, these workers (Christensen and Möller, 1975b) discovered that oral administration of nickel in 9 of 12 of the earlier subjects aggravated the condition, while intense handling of nickel-containing objects was without effect. The level of nickel ingested was approximately 5 mg. Although this level seems excessively high in light of commonly reported dietary levels of 300 to 600 μg Ni/day, the authors noted that the value was at the high end of dietary intake of a comparison population from a community near the clinic where the patients reported (mean: 0.76 mg; range: 0.20 - 4.46 mg).

The role of oral nickel in dermatitic responses was also demonstrated by Kaaber et al. (1978), who investigated the effect of a low nickel diet in patients with chronic nickel dermatitis manifested as hand eczemas of dyshidrotic morphology. Of 17 subjects in the clinical trial, nine showed significant improvement during a period of six weeks on a low nickel diet. Of these nine showing improvement, seven had a flare-up in their condition when placed on a normal diet. Furthermore, there was no correlation apparent between the level of urinary nickel and the degree of improvement following the diet. These authors recommended limitation in dietary nickel as a help in the management of nickel dermatitis. In this connection, Rudzki and Grzywa (1977) described an individual having chronic flare-ups in nickel dermatitis whose chronicity of condition was traced to the nickel content of margarine, Polish margarine having a rather high nickel content, up to 0.2 mg Ni/kg.

More recent studies have confirmed that dietary nickel is definitely a factor in nickel dermatitis flare-ups in a sizable fraction of the nickel-sensitive population (Jordan and King, 1979; Cronin et al., 1980; Christensen et al., 1981; Veien et al., 1983a). The data of Jordan and King (1979) and Cronin et al. (1980) indicate a dose-response relationship between flare-ups of hand eczema in nickel-sensitive patients and level of dietary nickel.

Sjöborg et al. (1984), using light and electron microscopy, studied the morphological changes of Langerhans cells in nickel dermatitis patients. Both normal skin and healed patch test areas were examined in subjects who experienced flare-up reactions induced by oral nickel administration. The authors found that, following oral administration of nickel, the cellular reactions took place in the topmost portion of the epidermis and were accompanied by formations of lipid-like inclusions in the Langerhans cells. Keratinocytes adjacent to the Langerhans cells had membrane and cytoplasmic changes.

As might be expected from the above discussions, control of dietary nickel ameliorates the frequency and severity of the allergenic response. In the study of Veien et al. (1983a), 23 of 33 patients who had flare-ups following oral challenge with nickel and other salts and were subsequently placed on low-metal allergen diets showed clearing or improvement of the condition after approximately four weeks.

The association between endogenous nickel and nickel sensitivity has prompted study of the known nickel chelant diethyldithiocarbamate, in the form of the dimer commercially available as Antabuse^R, for the management of flare-ups. In the double-blind, placebo-controlled study of Kaaber et al. (1983), 24 subjects with hand eczema and nickel allergy were given graduated doses of the agent (up to 200 mg) for a period of six weeks. The treatment group showed a significant reduction in the number of flare-ups and the extent of skin scaling ($p < 0.05$) compared to controls. In the similar but uncontrolled study of Christensen and Kristensen (1982), 11 patients given Antabuse^R (200 mg/day, 8 weeks) showed healing in two cases and improvement in eight patients. Relapses were observed in all patients 2 to 16 weeks after discontinuation of the drug. In both studies, hepatotoxicity was observed in some patients as a side effect of treatment.

While Kaaber et al. (1978) found little correlation between nickel excretion and the status of dermatitis in their patients, Menne and Thorboe (1976) reported elevated urinary nickel levels during dermatitis flare-ups. deJongh et al. (1978) found limited correlation between plasma nickel level, urinary excretion of nickel, and the clinical activity of the condition in a patient followed during two periods of five and six weeks each. More recent reports of Kaaber et al. (1979) and Christensen and Lagesson (1981), however, indicate that urinary nickel is a more reliable indicator of nickel intake, at least under conditions of challenge involving a sizable amount of the element.

Internal exposures to nickel associated with nickel sensitivity and arising from prosthesis alloys have been reviewed (Fisher, 1977; National Academy of Sciences, 1975; Samitz and Katz, 1975), and many of these data will only be summarized in this section.

The most common prosthesis alloys are stainless steel or cobalt-chromium (Vitallum), which may contain nickel in amounts up to 35 percent, but generally range between 10 to 14 percent (Samitz and Katz, 1975).

Instances of allergic reactions, as well as urticarial and eczematous dermatitis, have been attributed to implanted prostheses with resolution of the condition after removal of the devices (National Academy of Sciences, 1975; Samitz and Katz, 1975). Apparently, sufficient solubilization of nickel from the surface of the material appears to trigger an increase in dermatitis activity. In support of this, Samitz and Katz (1975) have shown the release of nickel from stainless steel prosthesis by the action of blood, sweat, and saline.

Fisher (1977), in his review, counseled caution in interpreting the reports and recommended specific criteria for proof of nickel dermatitis from a foreign body to include evidence of surface corrosion and sufficient corrosion to give a positive nickel spot test.

Nickel dermatitis has been described in a patient undergoing hemodialysis (Olerud et al., 1984). Exposure occurred through blood contaminated by nickel which had leached from a stainless steel fitting. Since nickel exposure can occur by various means for hemodialysis patients (Savory et al., 1985; Hopfer et al., 1985), as noted earlier in Chapter 4, allergenic responses may be a potential problem in these individuals.

Determination of nickel dermatitis classically involves the use of the patch test and site response to a nickel salt solution or contact with a nickel-containing object. The optimal nickel concentration in a patch test solution is set at 2.5 percent (nickel sulfate). Patch test reactions may be ambiguous in that they can reflect a primary irritation rather than a preexisting sensitivity (Uehara et al., 1975). Intradermal testing as described by Epstein (1956) has also been employed, but the procedure appears to offer no overall advantage to the conventional method (National Academy of Sciences, 1975).

The effect of nickel on lymphocyte transformation and the utility of this phenomenon as an *in vitro* alternative to conventional patch testing with its attendant ambiguity and dermatological hazards merit discussion.

Transformation of cultured human peripheral lymphocytes as a sensitive *in vitro* screening technique for nickel hypersensitivity versus the classical patch testing has been studied in a number of laboratories, and the earlier conflicting studies have been reviewed (National Academy of Sciences, 1975). The studies of Svejgaard et al. (1978), Gimenez-Camarasa et al. (1975), Millikan et al. (1973), Forman and Alexander (1972), and Hutchinson et al. (1972) have, however, established the reliability of the technique.

Nordlind and Henze (1984) found that nickel II (7.6 to 76 μM) stimulated both immunologically immature thymocytes and immunocompetent peripheral lymphocytes in children of different ages. Nickel-stimulated DNA synthesis in both of these systems occurred at a lower rate than did synthesis stimulated by the lectinic mitogens phytohaemagglutinin, concanavalin A, and pokeweed mitogen. DNA synthesis appeared to decrease with age in children ranging from 6 to 13 years of age.

The comparable value of the leukocyte migration inhibition test as an alternative technique remains to be demonstrated conclusively (MacLeod et al., 1976; Jordan and Dvorak, 1976; Thulin, 1976).

The induction of nickel sensitivity in human subjects has been claimed by Haxthausen (1936) and Burckhardt (1935). In their subjects, prior sensitivity was not ruled out. Furthermore, the concentration of the sensitizing solution, 25 percent, may easily have induced an irritation response. Later, Vandenberg and Epstein (1963) successfully sensitized nine percent (16 of 172) of their clinical subjects.

One area of controversy with regard to nickel dermatitis involves the question of hypersensitivity to groups of metals, i.e., cross sensitivity, and various sides of the issue have been reviewed (National Academy of Sciences, 1975). Of particular concern is the existence of hypersensitivity to both nickel and cobalt, as the elements occur together in most of the commodities with which susceptible individuals may come in contact. In a study by Veien et al. (1983b), 55 of 202 patients with hand eczema showed sensitivity to oral challenge of either nickel, chromium, or cobalt salt. The authors found that reaction sensitivity was no greater for ingestion of mixtures of the metals than that for individual salts, suggesting that cross sensitivity was not common in this particular patient group.

The underlying mechanisms of nickel sensitivity presumably include: (1) diffusion of nickel through the skin, (2) subsequent binding of nickel ion with protein(s) and other skin components, and (3) immunological response to the nickel-macromolecule complex (National Academy of Sciences, 1975). In the section on nickel metabolism, it was noted that penetration of the outer skin layers by nickel does occur. Jansen et al. (1964) found that nickel in complex with an amino acid (D,L-alanine) was a better sensitizer than nickel alone, while Thulin (1976) observed that inhibition of leukocyte migration in ten patients with nickel contact dermatitis could be elicited with nickel bound to bovine and human serum albumin or human epidermal protein, but not with nickel ion alone. Hutchinson et al. (1975) noted nickel binding to lymphocyte surfaces from both sensitive and control subjects; thus, nickel binding, per se, is not the key part of the immunological response (lymphocyte transformation). Braathen and co-workers (1983) investigated HLA-antigen profiles in patients with nickel dermatitis and found no association between HLA-A,B,C, or DR and active nickel allergenicity. Similar results have been noted by Karvonen et al. (1984).

5.2.1.2 Epidemiological Studies of Nickel Dermatitis. There are no studies of general populations which relate nickel exposures or levels in tissues and fluids to physiological, subclinical or clinical changes. The studies previously cited do not cover properly designed and executed samples of either total populations or selected population segments which would permit projection of findings to the total population from which subjects were selected. Only some industrially-exposed worker populations have been surveyed or monitored in any statistically adequate manner, and these studies will be reported later in connection with nickel carcinogenesis. The literature on adverse health effects in relation to nickel exposure for the general population is limited to the investigation of nickel dermatitis and nickel sensitivity, with only occasional reports related to other diseases or conditions. These latter are so fragmentary that they will not be considered.

5.2.1.2.1 Nickel sensitivity and contact dermatitis. Nickel dermatitis and other dermatological effects of nickel have been documented in both nickel worker populations and populations at large (National Academy of Sciences, 1975). Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological picture of nickel sensitivity offers ample proof that it is a problem among individuals not having occupational exposure to nickel but encountering an increasing number of nickel-containing commodities in their every-day environment.

There has been only one population survey using a probability sample to determine the incidence or prevalence of this allergic condition and its clinical manifestation, contact dermatitis. The literature is mostly limited to studies of patient populations, and this provides an unreliable basis for projection to the general population. Patient populations in specialty clinics are either self-selected and represent individuals who have decided that their condition is severe enough to require medical care or are those who have access to medical care and have been referred to specialty clinics. The perception of need for medical care for specific health problems varies significantly by socio-demographic characteristics. For example, a hairdresser or manicurist with dermatitis of the hands will seek medical care, while a factory worker or clerical worker with the same condition may not do so simply because there are no clients who object. The data presented here, therefore, are of limited value in assessing the distribution of sensitivity in the general population.

Large-scale surveys (Table 5-1) of patient populations were conducted by the International Contact Dermatitis Group (Fregert et al., 1969), the North American Contact Dermatitis Group (1973), and Brun in Geneva (Brun, 1975). Veien et al. (1982) reported on all pediatric patients in their clinic, 14 years or younger, who presented with contact dermatitis within a five-year period. Peltonen (1979) and Prystowsky et al. (1979) departed from the practice of surveying patient samples to surveying subjects more representative of the general population.

TABLE 5-1. RATES OF POSITIVE REACTORS IN LARGE PATIENT AND POPULATION STUDIES

Study and location	All subjects		Females		Males		Percent nickel sulfate
	number	percent reactors	number	percent reactors	number	percent reactors	
Fregert et al., Europe (1969)	4825	6.7	NS[a]	9.9	NS	1.8	5.0
North American Contact Dermatitis Group, USA and Canada (1973)	1200	11.2	691	14.9	509	5.5	2.5
Brun, Geneva (1975)	1000	12.2	NS	NS[b]	NS	NS	3.0
Peltonen, Finland (1979)	980	4.5	502	8.0	478	0.8	5.0 adults 2.5 children
Prystowsky et al., San Francisco (1979)	1158	5.8	698	9.0	460	0.9	2.5
Veien et al., Denmark (1982)	168	19.0	NS	NS	NS	NS	NS

[a] NS - not stated

[b] "higher than men"

All of these studies found that nickel sensitivity is one of the more common ones when standard test kits covering large numbers of substances are used, or when selected smaller numbers of allergens are used. Females always show a higher positive reaction rate than do males, and elicitation of contact history reveals universal exposure to the ubiquitous metal and its compounds.

The North American Contact Dermatitis Group study (1973) permits examination of race as a factor in positive reaction rates. As Table 5-2 shows, blacks have a higher rate than whites, and the females in either racial group have higher reaction rates.

A history of eczema is common in persons with positive reactions. Table 5-1 shows a summary of findings from large scale studies. The finding of particular interest is that nickel sensitivity appears as frequent in "general" population studies as in patient population studies, and it provides more certainty to the finding that large segments of the population, and females in particular, are at risk for this condition.

Table 5-3 shows, for a range of studies, the proportion of nickel sensitive persons who have a history of eczema of the hand and who reacted in kind to testing. This suggests that nickel sensitivity is by no means a negligible problem for a large proportion of those who exhibit the sensitivity.

Spruit and Bongaarts (1977a) investigated the relationship of nickel sensitivity to nickel concentrations in plasma, urine, and hair and found no association. The role of atopy, either personal or familial, in nickel-sensitive and nonsensitive dermatitis cases was examined by Wahlberg (1975). No differences of rates of personal or familial atopy were found for nickel-sensitive and nonsensitive patients with hand eczema. All cases were hairdressers; they showed a positive reaction rate of 40 percent to nickel sulfate (5 percent) solution. Wahlberg's finding for atopy are in accord with the earlier work by Caron (1964).

Spruit and Bongaarts (1977b) and Wahlberg (1975) reported that positive reaction to nickel sulfate occurs at very low dilution levels in some individuals. Wahlberg found 5 of 14 positive reactors sensitive to ≤ 0.039 percent nickel sulfate solution. Spruit and Bongaarts (1977b) found one female patient with a positive reaction when the solution was 10 µg Ni^{++}/l.

Edman and Möller (1982) reported on a University of Lund patient population of 8,933 who had been patch tested at the University clinic over a 12-year period. The authors found that nickel sensitivity increased during that period

TABLE 5-2. NORTH AMERICAN CONTACT DERMATITIS GROUP PATCH TEST RESULTS FOR 2.5 PERCENT NICKEL SULFATE IN 10 CITIES

Subject		Total No.	Positive Reactions	
			No.	Percent
Black	Females	79	14	17.7
	Males	64	6	9.3
	Total	143	20	14.0
White	Females	612	89	12.7
	Males	445	22	4.4
	Total	1057	111	10.5
All	Females	691	103	14.9
	Males	509	28	5.5
Total		1200	131	11.2

Source: North American Contact Dermatitis Group (1973).

TABLE 5-3. HAND ECZEMA IN PERSONS SENSITIVE TO NICKEL

Author	Nickel sensitive	Hand eczema	
		No.	Percent
Bonnevie (1939)	63	32	50.2
Wilson (1956)	85	14	16.5
Calnan (1956)	400	81	20.0
Fisher and Shapiro (1956)	40	16	40.0
Wagmann (1959)	62	22	35.0
Marcussen (1960)	621	272	43.2
Wahlberg and Skog (1971)	53	41	77.3
Cronin (1972)	84	50	60.0
Christensen and Möller (1975a,b)	185	96	52.0
Peltonen (1979)	44	9	20.5

Source: Adapted from Peltonen (1979).

for both male and female patients and that females had a higher rate of positive reactions than males.

Menné et al. (1982) reported on a stratified sample of the female population of Denmark surveyed by interview in 1978. The response rate was 77.4 percent. Of those responding, 14.5 percent reported a history of nickel allergy. The authors found that the prevalence rate was highest in the younger age groups and declined after the age of 50 (range: 16 to 99 years). Although the authors noted that use of the interview as an investigative technique had certain limitations, they believed it was the only realistic way to obtain data on a large and geographically widespread population and noted that their results were in agreement with data obtained through more conventional testing (e.g., patch testing) methods.

The avoidance of contact with nickel suggests itself as an obvious preventive measure. Kaaber et al. (1978) reported encouraging results in attempts to manage chronic dermatitis by reduction of nickel intake via the diet. However, total avoidance of contact with nickel would be extremely difficult, as it is commonly found in articles and substances found in the home and in metals used for jewelry, metal fasteners of clothing, coinage, and so forth. Some preparations used in hairdressing contain nickel, and consequently hairdressers exhibit nickel dermatitis. The consequences of nickel contact dermatitis seem to vary with the surrounding social factors. Male factory workers appear not to be handicapped by it (Spruit and Bongaarts, 1977b) and continue in their work; hairdressers leave their occupation when they develop dermatitis (Wahlberg, 1975).

The impact of nickel dermatitis on the health of the total U.S. population cannot be assessed at this time since the prevalence of this condition in the population is not established. Also, there are no data on the range of severity, the consequences, and the costs of the condition.

5.2.1.2.2 Sensitivity to nickel in prostheses. Stainless steel, chrome, and other metal alloys used in prostheses and other surgical devices frequently contain proportions of nickel that have proved to cause reactions in patients ranging from itching to dermatitis to tissue breakdown requiring replacement of the device. The National Academy of Sciences report (1975) lists the following devices and prostheses reported in the literature as associated with adverse reactions to their nickel contents: wire suture materials, metallic mesh for nasal prostheses, heart valves, intrauterine contraceptive devices, batteries for implanted pacemakers, alloys for dental castings and fillings, and orthopedic implants.

The alloys, contrary to general assumption, appear not to be biologically inert and produce adverse reactions in some of the individuals sensitive to nickel. A number of cases have been reported in which individuals developed malignant soft-tissue tumors near the implantation sites of bone plates or joint protheses containing nickel, chromium or cobalt (Linden et al., 1985).

Deutman and colleagues (1977) reported on metal sensitivity before and after total hip arthroplasty in 212 cases from their orthopedic service in Groningen, The Netherlands. They instituted their study because they noted that the recent literature contained reports of reactions to orthopedic implants which included loosening of total joint prostheses. The authors studied the preoperative sensitivity status of 212 patients scheduled for total hip replacement and followed up these patients to ascertain if sensitivity developed after the insertion. Fourteen patients were sensitive to one or more of three metals tested and eleven of these were sensitive to nickel. The allergens used were those recommended by the International Contact Dermatitis Group, that is, for nickel sensitivity, a 2.5 percent nickel sulfate solution was employed in the patch test. The past experience with metallic appliances for bone surgery was found to be 173 cases without previous experience, 17 cases with less than total joint replacement, 16 with total joint replacement and subsequent loosening and reoperations, and six with stable McKee-Farrar prostheses. Of the eleven nickel-sensitive patients, three had previous implants. Histories of nickel sensitivity showed five cases of eczema due to jewelry or garters and two cases with previous implants where the eczema appeared over the scar tissue of the site of the implant. Four individuals with positive reaction to the nickel allergen did not have a previous history of eczema. In addition, there were five patients with a history of sensitivity but no positive reaction to the patch test.

A second phase of the study consisted of 6 postoperative patch-testing of 66 of the 198 patients that had not exhibited preoperative sensitivity to patch tests. There were 55 women and 11 men with an average age of 69.5 years in this group. Four of these 66 showed metal sensitivity, three to nickel and one to cobalt. This included one woman with a negative preoperative patch test but who had a history of eczema from garters and who was positive on the postoperative patch test. None of the 66, regardless of sensitivity status, had shown pain, loosening of the prosthesis, infection, or skin symptoms during the postoperative period of the study which was approximately two years. This represented a postoperative conversion rate of six percent within approximately two years. A sensitivity rate of 4.6 percent to nickel by patch test was found in the 173 patients without previous bone surgery.

Since the publication of the National Academy of Sciences report, additional reports have appeared augmenting the list of items which have created sensitization and symptoms.

This special area of exposure via nickel in prostheses is of grave concern to the medical specialties and the patients involved, and is manageable to some extent by preoperative testing for sensitivity and routine elimination of nickel alloys.

5.2.1.3 Animal Studies of Nickel Sensitivity. Useful experimental animal models of nickel sensitivity have only slowly been forthcoming and only under very specialized conditions.

Nilzén and Wikstrom (1955) reported the sensitization of guinea pigs to nickel via repeated topical applications of nickel sulfate in detergent solution. Samitz and Pomerantz (1958), however, attributed this to local irritation rather than true allergenic response. Samitz et al. (1975) were unable to induce sensitization in guinea pigs using any nickel compound from complexation of nickel ion with amino acids or guinea pig skin extracts.

Wahlberg (1976) employed intradermal injection of nickel sulfate in highly sensitive guinea pigs. The reactions to the challenge were statistically greater than with control animals. Turk and Parker (1977) reported sensitization to nickel manifested as allergic-type granuloma formation. Sensitization required the use of a split-adjuvant treatment consisting of Freund's complete adjuvant followed by weekly intradermal injections of 25 μg of the salt after two weeks. Delayed hypersensitivity reactions developed in two of five animals at five weeks. Interestingly, these workers also observed suppression of the delayed hypersensitivity when intratracheal intubation of nickel sulfate was also performed on these animals (Parker and Turk, 1978).

Various attempts to sensitize mice to nickel have also been described. Möller (1984) found that, while mice could easily be sensitized to such potent antigens as picryl chloride, response to nickel could only be achieved by repeated epicutaneous application of a strong (20 percent) nickel salt solution for a three-week interval. The resulting dermatitis was moderate, as indicated by a weak wet weight increase in inflamed skin tissue.

5.2.2 Respiratory Effects of Nickel

Effects of nickel in the human respiratory tract, other than carcinogenicity, mainly derive from studies of nickel workers in various production categories who have been exposed to various forms of the element. In the aggregate, assessment of available clinical and animal data show two areas of concern for humans: (1) direct respiratory effects such as asthma manifested as either a primary irritation or an allergenic response; and (2) increased risk for chronic respiratory tract infections secondary to the effect of nickel on the respiratory immune system.

The acute effects of nickel carbonyl on the lung in man and experimental animals were summarized earlier (Section 5.1). Few data are available on the chronic respiratory effects of this agent except for one case described by Sunderman and Sunderman (1961) in which a subject exposed to low levels of the carbonyl developed asthma and Löffler's syndrome, a condition characterized by fever, cough, breathlessness, anorexia, and weight loss, and associated with eosinophilia and granulomatous tissue.

Available data on chronic noncarcinogenic effects of nickel compounds are mainly concerned with the soluble nickel (II) sulfate employed in electroplating operations and present as aerosols. Under heavy exposure conditions, anosmia and severe nasal injury such as septal perforation have been commonly observed, as well as chronic rhinitis and sinusitis (Tatarskaya, 1960; Kucharin, 1970; Sushenko and Rafikova, 1972).

Asthmatic lung disease in nickel-plating workers has also been documented (Tolat et al., 1956; McConnell et al., 1973; Malo et al., 1982; Block and Yeung, 1982; Cirla et al., 1985). In an occupational survey report of Cirla et al. (1985), 14 workers studied in the nickel-plating industry had rhinitis and/or asthma. Six subjects who showed a typical allergic response were workers in particular stages of the plating process. Dolovich et al. (1984) documented that occupational asthma in a nickel worker, as established by skin test and inhalation challenge, was associated with an antigenic determinant comprised of divalent nickel bound to human serum at a specific copper/nickel transport site. Similarly, Novey and co-workers (1983) evaluated a metal plater exposed to nickel sulfate who developed a biphasic asthma-like response. Specific IgE antibodies to nickel were also observed in the worker, leading the authors to believe that an IgE Type 1 immunopathogenic mechanism was involved in mediating the bronchial response.

While asthma appears to be most recognized in nickel plating operations, asthma has also been documented in welders. Keskinen et al. (1980) examined seven stainless steel welders suffering from respiratory distress during work and established that their distress was due to IgE-mediated chromium and nickel sensitivity.

Numerous studies of noncarcinogenic respiratory responses in experimental animals inhaling various forms of nickel have been reported. Bingham et al. (1972) exposed rats to aerosols of both soluble (as the chloride) and insoluble (as the oxide) nickel at levels in the region of those acceptable for human industrial exposure. Hyperplasia of bronchiolar and bronchial epithelium with peribronchial lymphocytic infiltrates was seen. Port et al. (1975) noted that intratracheal injection of a suspension of nickel oxide (5 mg, < 5 µm) into Syrian hamsters first treated with influenza A/PR/8 virus 48 hours previously, significantly increased mortality versus controls. Surviving animals at this dosing and lesser doses showed mild to severe acute interstitial infiltrate of polymorphonuclear cells and macrophages several weeks later. Additional pathological changes included bronchial epithelial hyperplasia, focal proliferative pleuritis and adenomatosis.

Wehner and co-workers (1981) studied hamsters inhaling nickel-enriched fly ash (aerosol, 17 or 70 µg/l) for up to 20 months. Lung weights and volumes were significantly increased in the higher (70 µg/l) fly ash exposure groups. The severity of anthracosis, interstitial reaction, and bronchiolization was dose-dependent.

Rabbits inhaling nickel chloride aerosol (0.3 mg/m^3 Ni) for 30 days showed changes (doubling) in cell number and volume of alveolar epithelial cells, as well as nodular accumulation of macrophages and laminated structures (Johansson et al., 1983). This effect pattern strongly resembled pulmonary alveolar proteinosis. These same workers (Johansson et al., 1981) investigated the lung response in rabbits inhaling metallic nickel dust (1 mg/m^3 Ni) for three and six months. In addition to responses similar to those noted above for soluble nickel aerosol, the six-month group showed pneumonia.

A number of studies have involved the cellular toxicity of nickel compounds as they relate to the incidence of infections in the respiratory tract, particularly the impairment of alveolar macrophage activity (Murthy et al., 1983; Wiernik et al., 1983; Lundborg and Camner, 1982; Casarett-Bruce et al., 1981; Castranova et al., 1980; Johansson et al., 1980; Aranyi et al., 1979; Adkins et al., 1979; Graham et al., 1975a; Waters et al., 1975).

At 1.1 mM nickel ion, rabbit alveolar macrophages show no morphological evidence of injury but apparently lose the ability for phagocytosis (Graham et al., 1975a). At 4.0 mM, cell viability is reduced to approximately 50 percent of controls (Waters et al., 1975).

Spiegelberg and co-workers (1984) exposed adult Wistar rats to nickel oxide aerosols for either four weeks or four months. Exposure levels for the short-term study were 50, 100, 200, 400, and 800 μg Ni /m^3, while exposure levels for the long-term study were either 25 or 150 μg Ni/m^3. Short-term effects on alveolar macrophages included altered size at the 100 μg Ni/m^3 level, increased phagocytic activity (elevated to 141 percent of controls) at the 400 μg Ni/m^3 level, and increased numbers of polynucleated cells, also at the 400 μg Ni/m^3 level. After four months of exposure, the number of macrophages was significantly increased at 25 μg Ni/m^3, but slowly decreased at 150 μg Ni/m^3. Increase in size and number of polynucleated macrophages was observed at both the 25 and 150 μg Ni/m^3 levels, and phagocytic activity increased to 130 and 230 percent of controls, respectively.

Several studies have examined the composition of lung fluid in animals inhaling various nickel compounds. Pulmonary lipid composition has been shown to be significantly altered in rabbits inhaling nickel dust (1.7 mg/m^3, 40 percent respirable) resulting in a threefold increase in phosphatidyl choline (Casarett-Bruce et al., 1981). Lundborg and Camner (1982) reported that significant decreases of lysozyme had occurred in rabbits inhaling nickel dust or nickel chloride after exposures to 0.1 mg/m^3 of metallic nickel and 0.3 mg/m^3 chloride salt for as little as three months. Hydrolytic enzymes in macrophages were significantly reduced in content, whereas the opposite occurred in macrophages of rats inhaling nickel oxide (120 μg/m^3) or nickel chloride (109 μg/m^3 (Murthy et al., 1983).

Aranyi et al. (1979) demonstrated that alveolar macrophage viability, total protein, and lactate dehydrogenase activity were significantly affected when nickel oxide was adsorbed into fly ash ranging in size from less than 2 μm to 8 μm. The effect increased with increased particle loading of nickel oxide and decreased particle size.

As recently discussed by Lundborg and Camner (1984), the overall effects of exposure to various forms of nickel on respiratory cellular defense mechanisms appear to resemble the pathological picture presented by both human pulmonary alveolar proteinosis and animals inhaling quartz dust.

Respiratory tract cytotoxicity of nickel species *in vitro* has also been examined. Dubreuil et al. (1984) found that treatment of human pulmonary epithelial cells (line A 549) with nickel chloride, at levels up to 1.0 mM, produced a dose-dependent decrease in cell growth rate, decreased content of ATP, and diminished viability. The levels of nickel employed were 0.1, 0.2, and 1.0 mM.

5.2.3 Endocrine Effects of Nickel

In different experimental animal species, nickel II ion has been shown to affect carbohydrate metabolism. Bertrand and Macheboeuf (1926) reported that the parenteral administration of nickel salts antagonized the hypoglycemic action of insulin. Later workers (Horak and Sunderman, 1975a and 1975b; Freeman and Langslow, 1973; Clary and Vignati, 1973; Kadota and Kurita, 1955) observed rapid, transitory hyperglycemia after parenteral exposure of rabbits, rats, and domestic fowl to nickel II salts. In several reports, Horak and Sunderman (1975a; 1975b) noted the effects of nickel II on normal, adrenalectomized, and hypophysectomized rats. Injection of nickel chloride (2 or 4 mg/kg) produced prompt elevations in plasma glucose and glucagon levels with a return to normal two to four hours afterwards, suggesting that hyperglucagonemia may be responsible for the acute hyperglycemic response to divalent nickel (Horak and Sunderman, 1975a). Nickel had the most pronounced hyperglycemic effect when this element was studied in conjunction with other ions given in equimolar amounts (Horak and Sunderman, 1975b). Concurrent administration of insulin antagonized this hyperglycemic effect. Kadota and Kurita (1955) observed marked damage to alpha cells and some degranulation and vacuolization of beta cells in the pancreatic islets of Langerhans. Ashrof and Sybers (1974) observed lysis of pancreas exocrine cells in rats fed nickel acetate (0.1 percent).

Human endocrine responses to nickel have been poorly studied, although Tseretili and Mandzhavidze (1969) found pronounced hyperglycemia in workmen accidentally exposed to nickel carbonyl.

Nickel apparently has an effect on the hypothalamic tract in animals, enhancing the release of prolactin-inhibiting factor (PIF) thereby decreasing the release of prolactin from bovine and rat pituitary glands (La Bella et al., 1973a). Furthermore, intravenous administration of small amounts of nickel to urethane-anesthetized, chlorpromazine-treated rats produces significant depression of serum prolactin without any affect on growth hormone or thyroid-stimulating hormone. The in vitro release of pituitary hormones other than PIF have been demonstrated for bovine and rat pituitary (La Bella et al., 1973b). In a more recent study, subcutaneous injection of nickel chloride (10 or 20 mg/kg) into rats first produced a drop in serum prolactin over the short term, but resulted in a sustained elevation of the hormone after one day, lasting up to four days (Clemons and Garcia, 1981). Elevation was due to reduced levels of prolactin-inhibiting factor. A later study by Carlson (1984), demonstrating that nickel II antagonizes the stimulation of both prolactin and growth hormone by barium II, suggested that the basis of antagonism may be competitive inhibition of calcium uptake.

Dormer and co-workers (1973; 1974) have studied the in vitro effects of nickel on secretory systems, particularly the release of amylase, insulin, and growth hormone. Nickel II was seen to be a potent inhibitor of secretion in all three glands: parotid (amylase), islets of Langerhans (insulin), and pituitary (growth hormone). Inhibition of growth hormone release at nickel levels comparable to those which La Bella et al. (1973b) observed to enhance release, may reflect differences in tissue handling prior to assay. Dormer et al. (1973) suggested that nickel may block exocytosis by interfering with either secretory-granule migration or membrane fusion and microvillus formation.

Effects of nickel on thyroid function have been noted by Lestrovoi et al. (1974). Nickel chloride given orally to rats (0.5 to 5.0 mg/kg/day, 2 to 4 weeks) or by inhalation (0.05 to 0.5 mg/m^3) significantly decreased iodine uptake by the thyroid, such an effect being more pronounced for inhaled nickel.

5.2.4 Cardiovascular Effects of Nickel

Recent studies, mainly involving experimental animal models, indicate that exogenous nickel II ion, under in vivo, ex vivo, and in vitro conditions, has a number of effects on the heart, including coronary vasoconstriction, myocardial depression, and subcellular injury.

Ligeti and co-workers (1980) reported that administration of nickel II ion at rather low levels (20 µg/kg body weight) to anesthetized dogs induced a significant decrease of coronary vascular conductance. Higher nickel dosing (200, 2000, and 20,000 µg/kg b.w.) caused further reduction of coronary blood flow and depression of heart rate and left ventricular contractility. Reduction of coronary blood flow was determined as arising from local action on coronary vessels.

Rubányi and Kovách (1980) observed that low levels of nickel II (0.01 to 1.0 μM) in the perfusate of the isolated rat heart increased coronary tone, while higher doses of the element depressed myocardial contractile performance. In related work, Rubányi et al. (1981) found that: (1) endogenous nickel was released from ischemic myocardium of dogs and rats using a nickel-complex cytochemical method, (2) exogenous nickel in amounts equivalent to that released endogenously induced coronary vasoconstriction in both the rat and dog heart, and (3) the cytochemical method was not affected by tissue autolysis. The basis of this vasoconstrictive activity appeared to involve a calcium-dependent mechanism (Koller et al., 1982). As a follow-up to their earlier studies, Rubányi and co-workers (1984) evaluated the effect of nickel on the *in situ* heart of anesthetized open-chest dogs. Soluble nickel ($NiCl_2$) was administered either intravenously (20 μg Ni/kg bolus injection) or via intracoronary infusion (40 μg Ni/min/kg). Rubányi and co-workers found that exogenous nickel at the reported levels of administration induced coronary vasoconstriction by direct action on coronary vessels. This vasoconstriction was induced when coronary arteries were dilated by low flow ischemia, arterial hypoxemia, and adenosine infusion. In addition, nickel inhibited vasorelaxation and postocclusion reactive hyperemia in response to arterial hypoxemia or infused adenosine. The authors postulated that vasoactivity might be related to the existence of positive feedback loops triggered by alterations in the level of nickel.

The release of endogenous nickel from damaged tissue and its implications for ischemic heart disease as described above have been examined in regard to the pathology of acute carbon monoxide poisoning and acute burn injury. According to Balogh et al. (1983), significant amounts of nickel were detected in autopsied heart muscle of human carbon monoxide poisoning victims or rats and dogs experimentally intoxicated with the agent when the Co-Hb fraction exceeded 30 percent. Rubányi et al. (1983) demonstrated that acutely burned rats showed significant accumulation of nickel in myocardium. In addition, focal myopathy, as characterized by intracellular edema, ruptured sarcoplasmic reticulum, and swelling/vacuolization of mitochondria with ruptured cristae, was also seen in this tissue. Isolated, perfused heart from burned animals showed significantly greater total coronary vascular resistance in terms of exogenous perfused nickel concentration when compared to controls at levels as low as 0.01 μM.

Human data relating nickel to the pathogenesis of cardiovascular disease states are meager. As noted above, Balogh et al. (1983) observed significant nickel accumulation in postmortem myocardium of carbon monoxide victims, paralleling the observation in experimental animals. Leach et al. (1985) noted that elevated serum nickel in patients with myocardial infarction does not relate to nickel exposure differences or to the biochemical indicators, serum CK or LDH activities, suggesting that hypernickelemia may be involved in the pathogenesis of ischemic myocardial injury. The existence of hypernickelemia in burn patients (see Chapter 4) and other traumatic states parallels the experimental data of Rubányi et al. (1983), who studied acutely burned rats.

The above experimental and clinical observations suggest that exogenous nickel II ion, and possibly endogenous nickel II, has a marked vasoconstrictive action on coronary vessels which could synergize the adverse effects of the primary ischemic lesion. As noted in the study of Rubányi and co-workers (1982) (Chapter 4), a huge transitory rise in serum nickel attending childbirth may be related to a minimizing of atonic bleeding. Care should be exercised in interpreting this study, however, owing to possible problems of analytical methodology and failure of other researchers (Nomoto et al., 1983) to replicate the results. Whether excessive nickel exposure in occupational or non-occupational populations exacerbates ischemic heart disease or enhances the risk of myocardial infarction in subjects with coronary artery disease is unknown. The presently available literature on mortality and morbidity of nickel workers for noncarcinogenic end points, specifically coronary artery disease, does not permit any conclusions on the matter, but the issue merits further study. Such study should also include populations living in the proximity of nickel operations.

Nickel subsulfide administered intrarenally in rats (5 mg/animal) induced arteriosclerotic lesions which were determined by inspecting hematoporphyrin derivative-injected arteries under ultraviolet light (Hopfer et al., 1984). Based upon various measurements of the chemical constituents of serum, it was determined that the observed arteriosclerosis was not associated with hypertension and hyperlipidemia.

5.2.5 Renal Effects of Nickel

Nickel-induced nephropathy in man or animals has not been widely documented. Acute renal injury with proteinuria and hyaline casts was observed by Azary (1879) in cats and dogs given nickel nitrate. Pathological lesions of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl (Hackett and Sunderman, 1967; Sunderman et al., 1961; Kincaid et al., 1953). Gitlitz et al. (1975) observed aminoaciduria and proteinuria in rats after single intraperitoneal injection of nickel chloride, the extent of the renal dysfunction being dose-dependent. Proteinuria was observed at a dose of 2 mg/kg, while higher dosing occasioned aminoaciduria. Ultrastructurally, the site of the effect within the kidney appears to be glomerular epithelium. These renal effects were seen to be transitory, abating by the fifth day. In rabbits, Foulkes and Blanck (1984) found that the nephrotoxic action of injected nickel salt ($NiCl_2$, 20 µmol/kg) was selective, being associated with reduced reabsorption of aspartate and having no effect on either glucose or cycloleucine reabsorption.

In man, nephrotoxic effects of nickel have been clinically detected in some cases of accidental industrial exposure to nickel carbonyl (Carmichael, 1953; Brandes, 1934). These effects are manifested as renal edema with hyperemia and parenchymatous degeneration.

5.2.6 Other Toxic Effects of Nickel

Nickel compounds appear to possess low neurotoxic potential save for fatal acute exposures to nickel carbonyl (National Institute for Occupational Safety and Health, 1977; National Academy of Sciences, 1975). Neural tissue lesion formation in the latter case is profound, including diffuse punctate hemorrhages in cerebral, cerebellar, and brain stem regions, degeneration of neural fibers, and marked edema.

Intrarenal injection of nickel subsulfide in rats elicits a pronounced erythrocytosis (Hopfer et al., 1980; Hopfer and Sunderman, 1978; Morse et al., 1977; Jasmin and Riopelle, 1976). Morse et al. (1977) showed that the erythrocytosis is dose-dependent, is not elicited by intramuscular administration, and is associated with marked erythroid hyperplasia of bone marrow. Hopfer and Sunderman (1978) observed a marked inhibition of erythrocytosis when manganese dust was co-administered. Sunderman et al. (1984) surveyed the erythrocytogenic potential of 17 nickel compounds given intrarenally to rats (7 mg/animal). Erythrocytosis was induced by nine of the agents: NiS, β-NiS, α-Ni_3S_2, Ni_4FeS_4, NiSe, Ni_3Se_2, NiAsS, NiO, and Ni dust. Rank correlation ($p < 0.0001$) was obtained between erythrocytosis and renal cancers. Erythrocytosis in this animal model of nickel toxicity appears to be mediated by enhanced erythropoietin production (Hopfer et al., 1985).

The effects of nickel chloride on the cellular and humoral immune responses of mice have been studied (Smialowicz et al., 1984; Smialowicz, 1985). Natural killer (NK) cells, lymphocytes thought to be one of the first lines of nonspecific defense against certain types of infection and tumors, were seen to be significantly suppressed in activity within 24 hours of a single intramuscular injection of nickel chloride (18.3 mg/kg) into mice. Nickel chloride was also shown to significantly decrease the percentage of T lymphocytes observed in the spleens of treated mice ($P < 0.05$). The results confirmed the works of others on the immunosuppressive effects of nickel on circulatory antibody titers to T_1 phage (Figoni and Treagan, 1975), on antibody response to sheep erythrocytes (Graham et al., 1975b), on interferon response of cells treated in vivo (Treagan and Furst, 1970), and on the susceptibility to pulmonary infections following inhalation (Adkins et al., 1979). Of particular importance were the effects on NK cells in light of their possible relation to tumor development.

5.3 INTERACTIVE RELATIONSHIPS OF NICKEL WITH OTHER FACTORS

Both antagonistic and synergistic interactive relationships have been demonstrated for both nutritional factors and other toxicants.

Co-administration of high doses of vitamin C to the weanling rat offset the effects of oral nickel exposure on growth rate, as well as the activity of certain enzymes, such as liver and kidney succinic dehydrogenase and liver glutamic-oxaloacetic transaminase (Chatterjee et al., 1980). According to Hill (1979), dietary protein antagonizes the effect of dietary nickel (as the chloride, 400 or 800 µg/g) on retarding growth in chicks over the range of 10 to 30 percent protein.

Ling and Leach (1979) studied element interaction in diets containing 300 mg/kg of nickel and 100 mg/kg of iron, copper, zinc, and cobalt. Indices of toxicity were growth rate, mortality, and anemia. The lack of interaction among these elements and nickel is in contrast to a protective effect of nickel for the adverse effects of copper deficiency (Spears and Hatfield, 1977). Presumably, the existence of any interactive mechanism is overwhelmed at large levels of agents employed in the former study.

Using lethality of injected nickel chloride (95 or 115 µmol/kg) in rats as an effect index, Waalkes et al. (1985) demonstrated that co-administration of zinc II (multiple doses, 300 µmol/kg) at different times significantly increased the 14-day survival rate. Administration of zinc II offset the extent of renal damage and hyperglycemia seen in animals exposed solely to nickel II. This protective action did not appear to be associated with induction of metallothionein, nor did it alter the excretion/distribution of the element.

According to Nielsen (1980), there is a nutritional interaction between iron and nickel in the rat which depends on the state (valence) and level of iron in the diet. Nickel supplementation offset reduced hemoglobin and hematocrit values in iron-deprived rats when the ferric ion was employed, but less so when divalent-trivalent iron mixtures were used. It is possible that the enhanced absorption of the trivalent iron was directly related to nickel.

Divalent nickel appears to antagonize the digoxin-induced arrythmias in intact and isolated hearts of rats, rabbits, and guinea pigs, doing so by either binding competition with calcium ion at cell membranes or provoking an increase in malic and oxaloacetic acid activity (Prasad et al., 1980).

Pretreatment of rats with nickel (6 mg Ni/kg, i.p., 3 daily doses) reduced the level of enzymuria, proteinuria, and aminoaciduria in rats exposed to cadmium ion (6 mg Cd/kg, i.m., single dose) (Tandon et al., 1984). This protection occurred without altering cadmium excretion or accumulation in liver and kidney.

In a study on the effect of nickel chloride on natural killer (NK) cell activity (Smialowicz, 1985), the authors also tested for the effects of manganese chloride. Unlike nickel chloride, manganese chloride was found to enhance NK cell activity, and this enhancement was associated with increased levels of circulating interferon. The authors reported that the manganese chloride had an antagonistic effect on nickel chloride-suppression of NK cell activity which might provide important clues to understanding the antagonism of manganese for nickel-induced carcinogensis.

Nickel ion combined with benzo(a)pyrene enhanced the morphological transformation frequency in hamster embryo cells over that seen with either agent used alone (10.7 percent, verses 0.5 percent and 0.6 percent for nickel and benzo(a)pyrene, respectively) at levels of 5 μg/ml nickel salt and 0.78 μg/ml benzo(a)pyrene. Furthermore, in a mutagenesis system using hamster embryo cells, as described by Barrett et al. (1978), a comutagenic effect between nickel sulfate and benzo(a)pyrene has also been observed (Rivedal and Sanner, 1980; 1981). These observations, supported by cocarcinogenic effects between nickel compounds and certain organic carcinogens (Toda, 1962; Maenza et al., 1971;

Kasprzak et al., 1973), are of considerable importance in evaluating the enhancing effect of cigarette smoke on the incidence of lung cancer in nickel refinery workers (Kreyberg, 1978).

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6. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF NICKEL

Various nickel compounds have been assessed for their effects on reproduction and the developing embryo/fetus. This chapter summarizes the pertinent literature related to the reproductive and developmental toxicity of nickel.

6.1 REPRODUCTIVE FUNCTION/FERTILITY EFFECTS

Ambrose et al. (1976) examined the effects of dietary administration of nickel sulfate hexahydrate in a three-generation reproduction study in rats. Males and females of the parent (F_0) generation were exposed to levels of 0, 250, 500, and 1000 ppm nickel, starting at 28 days of age. Mating within dose groups was initiated after 11 weeks of feeding. The first generation consisted of two groups of offspring, F_{1a} and F_{1b}, derived from the single F_0 generation. For the second and third generations, breeding pairs from dams and sires exposed to nickel in F_{1b} or F_{2b}, respectively, were placed on the same diet; and progeny from these matings were carried through the same protocol as the F_1 generation. Consequently, all generations comprised two groups of offspring.

Exposure to 250 or 500 ppm diets had no effect on body weight of the parents when measured before mating and at weaning. Body weight was lower following exposure to 1000 ppm ($\leq$8 percent in females, $\leq$13 percent in males). No other signs of toxicity in the parental animals were reported. In a concurrent two-year chronic feeding study, rats exposed to 1000 ppm and above showed changes in organ-to-body weight ratios for liver and heart.

As regards reproductive function and fertility, the authors reported no effect on fertility, pregnancy maintenance, or postnatal survival of the offspring throughout the three generations. There was a consistent reduction in offspring body weight at weaning in the 1000 ppm group in all three generations, although the authors note that the animals "recovered considerably" by the time they were mated. Unfortunately, statistical analysis of this and the other reproduction data is lacking. Furthermore, the body weight reductions and "recovery" are not distinguished by sex; thus, sex differences in growth may obscure the significance of these observations. Considering these points and the reduced parental body weight at this dose, the effect of nickel exposure on postnatal growth cannot be assessed. Other observations included an increase in fetal death in both groups of the first generation (but not subsequent generations) and a possible decrease in litter size and postnatal survival. However, the authors do not discuss these data relative to reproductive toxicity, and with the lack of statistical analysis, the significance cannot be determined.

Schroeder and Mitchener (1971) also exposed three generations of rats to drinking water which contained nickel (5 ppm) as an unspecified soluble salt. In each of the three generations, the animals exposed to nickel gave birth to litters which exhibited a significantly increased perinatal mortality, and there was a significantly increased number of "runts" in the first and third generations. There also appeared to be a generation-related decrease in both litter size and male:female ratios.

Phatak and Patwardhan (1950) added nickel at levels of 250, 500, or 1000 ppm in the diets of male and female albino rats. Nickel was supplied either as metallic nickel, as nickel carbonate, or as a "nickel soap" (a material derived by mixing nickel carbonate with a mixed fatty acid solution obtained from refined groundnut oil). There appeared to be an effect on growth in the parental animals during eight weeks exposure prior to mating at 1000 ppm. Due to deficiencies in the experimental design relative to sample size and statistical analysis, it is difficult to discriminate potential differences between treated and control groups. However, the limited data do suggest that the litter size from rats treated with 1000 ppm nickel may have been smaller than in controls.

6.2 MALE REPRODUCTIVE SYSTEM EFFECTS

Hoey (1966) examined the effects of a number of metallic salts on the testis and epididymis of male rats. The lack of appropriate controls and the incomplete description of the methods make analysis of the experiment difficult; however, the resultant histology demonstrated an effect of nickel. In acute studies, male rats received a single, subcutaneous injection of 0.04 mmol/kg nickel sulfate, 18 hours to 12 days before sacrifice. By 18 hours postexposure, there was marked damage to the seminiferous tubules, but no effect on the interstitial tissue. Within the epididymis, there was some shrinkage and the spermatozoa were completely degenerated. By day 12 postexposure, most of the histopathological changes were no longer evident; however, spermatogenesis remained very limited. Under multiple exposure conditions, the exposure level and types of effects relative to time of exposure are unclear from the description. However, in general, degenerative changes similar to those following acute exposure were reported.

Mathur et al. (1977) examined dermal exposure of male rats to nickel sulfate, applying concentrations of 40, 60, and 100 mg Ni/kg daily, for up to 30 days. There were no clinical signs of general toxicity or mortality. There were no macroscopic changes in skin, liver, kidney, or testis. Histologically, the testis exhibited tubular damage and sperm degeneration following exposure to 60 mg Ni/kg for 30 days, and these effects were more dramatic at the 100 mg Ni/kg level. The liver also showed signs of toxicity at this exposure level/duration. There was no effect on the testis at 40 mg Ni/kg for 30 days or at any exposure level when applied only for 15 days. Thus, the toxic effects appear related to both level and duration of exposure. The authors note the similarity of their results with those of Hoey (1966) and von Waltschewa et al. (1972)[1]. Mathur and co-workers (1977) point out that dermal exposure (as assessed in their study) appears to permit appreciable absorption of nickel, and therefore may be a significant route of exposure in specific occupational settings.

Other studies have also provided evidence to support nickel's toxicity in the reproductive system of male mice. Jacquet and Mayence (1982) intraperitoneally injected male BALB/c mice with 40 or 56 mg/kg of nickel nitrate in saline and then mated the treated males or control males (treated with saline only) to superovulated females for a five-week period. Pregnant females were sacrificed, and isolated, viable embryos (which were undergoing cleavage) were cultured in Brinster's medium for a total of three days. The embryos were scored for their ability to develop to the blastocyst stage. The results indicated that a dose of 40 mg/kg did not affect the fertilization capacity of the spermatozoa or the ability of the fertilized eggs to cleave. However, the dose of 56 mg/kg yielded a significant proportion ($p \leq 0.01$) of uncleaved (unfertilized) eggs which were incapable of developing into blastocysts. Cleaved eggs from this same dose group were capable of developing into blastocysts. Because treatment with nickel did not affect the ability of those embryos which were fertilized to develop to the blastocyst stage, the authors suggested that treatment with 56 mg/kg nickel had a toxic effect on the process of spermatogenesis.

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[1] Original manuscript not available during this review.

Deknudt and Leonard (1982) performed a dominant lethal test for nickel chloride and nickel nitrate in BALB/c mice. Neither nickel compound produced an increase in postimplantation death; however, both were associated with a decreased rate of pregnancy and an increase in the preimplantation loss of embryos. The data suggest that these nickel-containing compounds may either affect the male reproductive tract or may have an effect on early preimplantation embryos. (For further discussion of these studies in regard to the induction of chromosomal aberrations, see Chapter 7.)

6.3 FEMALE REPRODUCTIVE SYSTEM EFFECTS

Studies on nickel-induced effects on the reproductive system of female animals are limited, but have demonstrated that the effects of nickel are not only seen in male animals. The effects of intrauterine devices on the viability of embryos or implantation of embryos into the endometrium have been tested. Chang et al. (1970) evaluated the ability of several metals within these devices to produce effects in rats and hamsters. Nickel was found to inhibit the fertility of rats as evidenced by a decrease in the number of implantations and an increase in the number of resorption sites in those uterine horns which had intrauterine devices made of nickel. These data suggest that nickel can affect both the ability of embryos to implant and the viability of recently implanted embryos.

6.4 DEVELOPMENTAL EFFECTS

Sunderman et al. (1978a) studied the effects of intramuscularly injected nickel chloride in Fischer 344 rats. A single acute injection was administered on gestational day 8 in doses of either 8, 12, or 16 mg/kg body weight. In a preliminary study, an LD_{50} of 22 mg/kg was established for treatment on gestation day 8, and the authors reported an LD_5 of 17 mg/kg. However, none of the three doses in the developmental toxicity study led to maternal death or altered gestation length. No other signs of maternal toxicity were reported. Treatment resulted in fetal effects at the two higher dosages which included decreased numbers of live pups per dam with increased ratios of dead fetuses to implantation sites. In addition, the mean fetal weights of the high dose group were statistically lighter than controls. When allowed to survive until eight weeks of age, the nickel-treated pups remained statistically lighter than controls. In a separate experiment, Sunderman et al. (1978a) investigated the effect of repeated doses of 1.5 or 2.0 mg/kg of nickel chloride per day on gestational days 6 through 10. Control dams were injected with an equal volume (0.4 ml) of sterile saline. Under this treatment regimen, the high dose group (2 mg/kg per day) exhibited a decrease in the mean number of live fetuses per dam and an increase in the ratio of dead fetuses to implantation sites; however, the mean body weights of the fetuses were not decreased.

Lu et al. (1979) administered a single acute intraperitoneal injection of nickel chloride to pregnant CD-1 mice on one of gestational days 7 through 11. On each of the gestational days, 7 experimental groups of animals were treated, including 6 nickel groups (1.2, 2.3, 3.5, 4.6, 5.7, or 6.9 mg/kg of nickel) and a vehicle control. Maternal death was associated with the 6.9 mg/kg exposure level on all treatment days, and with 4.6 mg/kg or above on gestation days 9, 10, or 11. No other signs of maternal toxicity were reported. There was a dose-related increase in fetal death on all treatment days, with apparent increases occurring even at the lowest dose tested (1.2 mg/kg). On all days of treatment, exposure to 4.6 mg/kg or higher resulted in a significant reduction in fetal weight and placental weight; similar reductions also occurred at 3.5 mg/kg on days 10 and 11. The authors also reported a dose-related increase in structural abnormalities, encompassing both the skeleton and soft tissue. The significance of this finding is obscured, however, since the percent or number of abnormal fetuses at each dose level and treatment time is not indicated. In addition, abnormalities occurred only at dose levels where fetal death occurred, and thus may be related to general fetotoxicity and not to a specific teratogenic action.

Other studies have also provided evidence to support the potential developmental toxicity of the aqueous nickel salts. Berman and Rehnberg (1983) administered 500 or 1000 ppm nickel chloride in drinking water to pregnant CD-1 mice during the period of gestational days 2 through 17. No effects were seen at the 500-ppm dose level; however, 1000 ppm nickel caused a loss in maternal weight, reduced mean birth weights of pups, and increased incidence of spontaneous abortions. Using a short-term, in vivo screen, Chernoff and Kavlock (1982) treated pregnant CD-1 mice with 30 mg/kg of nickel chloride intraperitoneally on gestational day 8. They concluded that nickel chloride was fetotoxic based on a decreased mean number of pups per litter compared to controls. In addition, the pregnancy rate for nickel-treated dams was significantly reduced (43 percent treated versus 53 percent controls). The authors did not report the presence of any malformations or variations in pups at day 20 of gestation. Finally, Ferm (1972) reported that intravenous administration of 30 mg/kg of nickel acetate to hamsters on day 8 of gestation produced fetal death and "general malformations," although the malformations were not described.

The potential developmental toxicity of aqueous soluble nickel salts has also been studied in the avian species. Nickel chloride hexahydrate was injected into fertile chicken eggs on either day four of incubation, via the yolk sac, or day eight of incubation, via the chorioallantoic membrane (Ridgway and Karnofsky, 1952). The doses used were 2.0 mg per egg on day 4 or 1.4 mg per egg on day 8. Nickel chloride was found to be embryolethal, but not teratogenic. The time of administration in this study was relatively late, however. In studies by Gilani (1982) and Gilani and Marano (1980), nickel chloride was injected into fertile chicken eggs at doses of 0.02 to 0.7 mg per egg on either day of incubation 0, 1, 2, 3, or 4. Control eggs were injected with an equal volume (0.1 ml) of sterile saline per egg. The embryos were sacrificed on day eight of incubation and examined grossly for malformations. Under these conditions, nickel chloride was found to induce a series of malformations which were dose-dependent; the highest incidence of malformations occurred on day two of incubation.

Storeng and Jonsen (1980, 1981) studied the effects of nickel on early embryogenesis in NMRI/Bom mice. Using an in vitro approach (Storeng and Jonsen, 1980), mouse embryos from the 2- to 8-cell stage were cultured in media which contained nickel chloride at concentrations of 10 to 1000 μM. Control media did not contain nickel. There was a dose-related effect on development to the morula stage of embryos exposed at the 2-cell stage, with effects observed at the lowest dose tested (10 μM $NiCl_2 \cdot 6H_2O$). When exposure was not initiated until the 4- to 8-cell stage, higher concentrations (200 to 300 μM) were required to cause an effect on development; no effect was observed at 100 μM.

In a subsequent in vivo study (Storeng and Jonsen, 1981), a single intraperitoneal injection of nickel chloride hexahydrate (20 mg/kg body weight) was administered to pregnant mice on one of gestational days one through six. The dams were sacrificed on gestational day 19 and gestational and embryotoxicity data were ascertained. The data presentation and statistical approach do not permit a clear interpretation of dose- and time-related effects. However, it does appear that in vivo exposure during this period of gestation may result in increased resorptions and gross structural defects.

The potential embryotoxicity and fetotoxicity of nickel subsulfide (Ni_3S_2) were examined by Sunderman et al. (1978a). Nickel subsulfide dust with a mean particle diameter of less than 2 µm was suspended in a volume of 0.2 ml penicillin G. The suspension of nickel subsulfide was injected intramuscularly at a dosage of 80 mg of nickel per kg of body weight on gestational day 6 into Fischer 344 rats. Control dams received 0.2 of penicillin G vehicle only. The nickel subsulfide treatment was determined to be embryotoxic to the rats based upon a reduction of the number of live fetuses per dam and an increase in the ratio of dead and resorbed fetuses to the total number of implantation sites. No skeletal or visceral anomalies were observed in the pups at term.

Sunderman et al. (1983) have also used intrarenal injection of nickel subsulfide in rats prior to mating in order to assess the potential effects of nickel subsulfide-induced maternal polycythemia on the offspring. Virgin female Fischer 344 rats were each given an intrarenal injection of 10 mg of nickel subsulfide suspended in saline. Seven days post injection the females were caged with virile males to mate. The dams were allowed to give birth to their young, which were examined on postnatal day three for possible gross malformations. Pups were allowed to survive until four weeks after birth, at which time they were weighed and blood samples were collected for evaluation of the hematocrit. Evaluation of the maternal data suggested that the intrarenal injection of nickel subsulfide did successfully induce maternal polycythemia and erythrocytosis in the dams but not in the offspring. These findings indicate that the release of maternal erythropoietin by the maternal kidneys, caused by nickel subsulfide, did not stimulate erythropoiesis in the pups. The postnatal hematocrits of the nickel-treated pups tended to be lower than those of the control pups during the first two weeks, although they did approach controls by the end of the experiment. Nickel subsulfide was associated with a decrease in mean pup weights of both male and female pups, both at birth and throughout the first postnatal month.

Finally, in a series of experiments, Sunderman and co-workers (1983, 1980, 1979, 1978b,c) exposed pregnant rodents (rats and hamsters) to varying levels of nickel carbonyl via inhalation or intravenous injection and observed both teratogenic and fetotoxic effects. In rats, a single exposure by inhalation on gestation day 7 to 0.16 mg/liter for 15 minutes resulted in decreased fetal viability and fetal weight, and an increased number of litters with malformations. Similar effects were seen at 0.30 mg/liter, but this level was also associated with significant maternal death. Lower exposure levels on day seven were not evaluated. On gestation day 8, fetal viability was reduced at 0.08 mg/liter/15 minutes (lowest level tested), and fetal viability and weight were reduced and malformations increased at 0.16 mg/liter. On day 9, 0.16 mg/liter/15 minutes caused reduced fetal viability and weight, but did not result in any malformations. In hamsters, inhalation exposure to 0.06 mg/liter for 15 minutes on gestation day 4 or 5 led to decreased fetal viability and increased numbers of litters (and fetuses) with malformations. Exposure on days six, seven or eight did not have a significant effect on development. Among the teratogenic effects noted were anophthalmia and microphthalmia in rats and exencephaly and cystic lungs in hamsters.

6.5 SUMMARY

The studies that have been reviewed indicate that exposure to nickel has the potential to cause reproductive and developmental toxicity in various experimental animals. In contrast to these studies, it should also be noted that the experiments of Nielsen et al. (1975, 1979) demonstrated that a deficiency of dietary nickel can also be associated with reproductive effects (See Chapter 9).

With respect to specific reproductive effects, exposure of male rats to nickel salts results in degenerative changes in the testis and epididymis and in effects on spermatogenesis. Limited studies in female rats and hamsters suggest an effect on embryo viability and the implantation process. In general, the studies reviewed provide sufficient data to indicate the potential for effects on the reproductive process. However, studies should be designed to cover a wider range of exposure levels and durations, in order to better define the exposure-response relationship for various reproductive endpoints. In addition, studies that focus on the female reproductive system should be carried out to expand the limited data base that is currently available.

With respect to developmental toxicity, nickel exposure of animals prior to implantation has been associated with delayed embryonic development and possibly with increased resorptions. Exposure following implantation has been associated with increased fetal lethality and resorptions and decreased fetal weight. Several studies using nickel salts reported an increase in structural malformations in the mammal or chick. However, in the mammalian studies, the manner of data reporting and lack of detail make it difficult to determine the significance of these findings. There is a teratogenic effect associated with exposure to nickel carbonyl, which Sunderman and co-workers reported in two species by two routes of exposure. Studies designed to establish the no-observed or lowest-observed effect level would aid in assessing the risk to humans relative to effects on embryo/fetal development, following exposure to this form of nickel.

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7. MUTAGENIC EFFECTS OF NICKEL

Various inorganic compounds of nickel have been tested for mutagenicity and other genotoxic effects indicative of mutagenicity in a variety of test systems ranging from microorganisms to human cells. This chapter includes an analysis of the pertinent literature pertaining to the mutagenicity and genotoxicity of these nickel compounds. For further information on the mutagenicity and genotoxicity of nickel compounds, the extensive reviews by Sunderman (1981, 1983) and Christie and Costa (1983) should be consulted.

7.1 GENE MUTATION STUDIES

7.1.1 Prokaryotic Test Systems (Bacteria)

Gene mutation studies of nickel compounds in bacterial systems are summarized in Table 7-1.

LaVelle and Witmer (1981), in an abstract of a paper presented at the Twelfth Annual Meeting of the Environmental Mutagen Society, claimed that nickel chloride ($NiCl_2$) was mutagenic in the *Salmonella typhimurium* TA 1535. They used a fluctuation test and a concentration range of 0.01 to 0.1 mg/ml of the test chemical. According to these authors, dose-related increases in the mutation frequency were noted. Ethylmethane sulfonate and dimethylsulfoxide (DMSO) were used as positive and solvent controls, respectively. Details of experimental data are not available in this abstract; hence, a critical evaluation of this study is not possible.

Green et al. (1976) investigated the mutagenic potential of nickel chloride using the *Escherichia coli* WP2 trp-fluctuation test. In the fluctuation test, where a reversion from auxotrophy to prototrophy takes place in culture tubes treated with the test compound, multiplication of the prototrophic revertants results in an increase of turbidity of the medium. The frequency of mutation can be determined by counting the number of turbid tubes. After treatment with nickel chloride at concentrations of 5, 10, and 25 μg/ml, mutation frequencies

TABLE 7-1. MUTAGENICITY EVALUATION OF NICKEL: GENE MUTATIONS IN PROKARYOTES

Indicator Organisms	Strain	Assay System	Test Compound	Concentration	Reported Response	Comments	Reference
Salmonella typhimurium	TA1535	Fluctuation test	Nickel chloride	0.01-0.1 mg/ml	+	Meeting abstract; no details.	LaVelle and Witmer (1981)
Escherichia coli	WP_2	Fluctuation test	Nickel chloride	5,10,25 μg/ml	-		Green et al. (1976)
Corne-bacterium	Homo-serine-dependent	Fluctuation test	Nickel chloride	0.031, 0.062, 0.125, 0.25, 0.5, 1, 5, 10 μg/ml	+	Preliminary study needs confirmation; dose-related increases in revertants only seen at levels ≥ 0.5 μg/ml.	Pikalek and Necasek (1983)

were similar to those of control groups. In the experimental groups there were 51, 42, and 27 turbid tubes, respectively, for the above doses. Controls showed 44, 44, and 51 turbid tubes. Two hundred tubes were scored for each concentration with 200 concurrent control tubes.

Pikalek and Necasek (1983) demonstrated the mutagenic effect of nickel chloride using the simplified fluctuation test and the clone test in a homoserine-dependent strain of Cornebacterium. Nickel chloride at concentrations of 0.031, 0.062, 0.125, and 0.25 µg/ml did not induce revertants. However, at concentrations of 0.5, 1.0, 5.0, and 10.0 µg/ml, dose-related increases in the number of revertants were obtained as shown in Table 7-2.

In the clone method the cells were treated with nickel chloride and incubated for 41 hours at 29°C on a reciprocal shaker. The cell suspension was diluted and spread on complete agar medium and minimal agar medium to select revertants. In the clone test, the nickel chloride caused a decline in the revertant frequency up to a concentration of 28 µg/ml. However, concentrations of 36 µg/ml and above yielded increased frequencies of revertants with a decrease in cell survival as shown in Figure 7-1.

Mutagenicity of nickel compounds in bacterial systems are considered inconclusive because of a lack of adequate data in the Salmonella assay and because the Cornebacterium assay requires further confirmation. However, these studies point out that variation in the sensitivity of bacterial strains plays an important role in testing metal compounds.

7.1.2 Eukaryotic Microorganisms (Yeast)

Gene mutation studies of nickel compounds in eukaryotic systems and cultured mammalian cells are summarized in Table 7-3.

Singh (1983) reported nickel sulfate ($NiSO_4$)-induced gene conversion and reverse mutations in the yeast Saccharomyces cerevisiae D7. Aliquots of cells were spread on complete growth medium. After the aliquots had dried, a center well was made in the agar medium and the well was filled with 0.1 M nickel sulfate. Plates were incubated overnight at 30°C. As the test compound diffused into the medium, a concentration gradient was produced and a zone of cell killing in the vicinity of the well demonstrated the toxicity of the test compound. The plates were replica plated onto medium lacking tryptophan and medium lacking isoleucine and valine. Gene conversion at trp and reverse mutation at ilv were indicated by a ring of colonies on the agar plates lacking

TABLE 7-2. THE MUTAGENIC EFFECT OF NICKEL CHLORIDE ON A HOMOSERINE-DEPENDENT STRAIN OF CORNEBACTERIUM

$NiCl_2$, mg/l	P	N	C	T	T%	X^2
0.031	3	99	11	10	10.1	-
0.062	5	165	25	30	18.1	-
0.125	5	165	25	25	15.1	-
0.25	5	165	25	30	18.1	0.54
0.5	6	198	27	50	25.2	8.52
1	2	66	10	21	31.8	5.10
5	5	165	43	158	96.3	172
10	3	99	29	99	100	108

P = number of experiments, N = total number of test-tube cultures in the control or test series, C = number of positive test-tube cultures in the control series, T = number of positive test-tube cultures in test series.

Source: Adapted from Pikalek and Necasek (1983).

tryptophan and isoleucine, respectively. Nickel sulfate showed a positive reaction to gene conversion and weak response to reverse mutation. However, this study was generally lacking in details and data were not presented to support the author's conclusion.

7.1.3 Mammalian Cells In Vitro

Miyaki et al. (1980) investigated the mutagenic potential of nickel chloride in cultured V79 Chinese hamster cells, at the hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) locus. The authors used a test that involves selection of presumed mutations that are resistant to 8-azaguanine. Normally, the wild type cells contain HGPRTase enzyme, which converts 8-azaguanine to toxic metabolites, resulting in cell death. However, spontaneous mutants and mutants induced by test chemicals do not contain active HGPRTase, and therefore grow in the presence of 8-azaguanine. Nickel chloride at concentrations of 0.4 mM (5 μg/ml) and 0.8 mM (10 μg/ml) induced 7.1 ± 0.2 and 15.6 ± 2.0 mutants per 10^6 survivors, respectively. The control mutation rate was

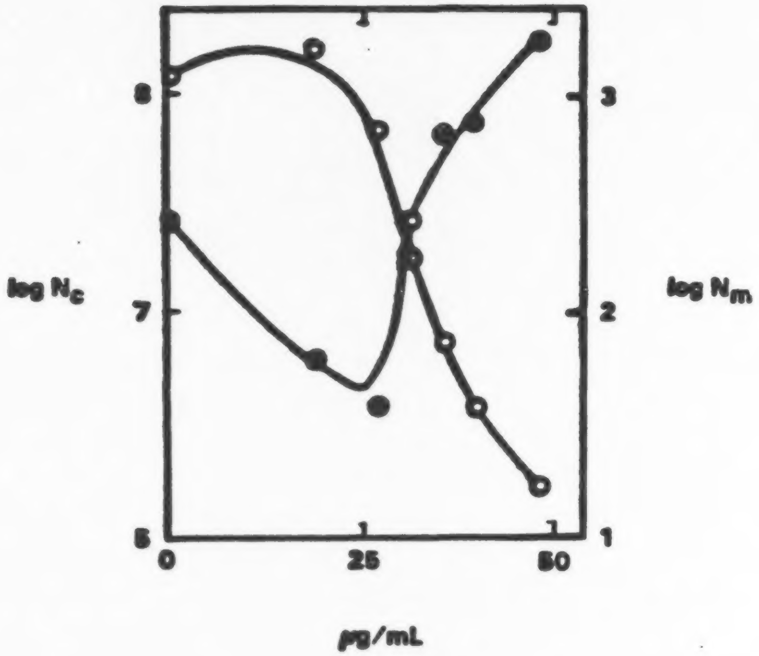

Figure 7-1. The relationship between the lethal and mutagenic effect of Ni^{2+} (μg/ml) by means of the clone method: N_c, number of surviving cells (open symbols); N_m mm (closed symbols) in 1 ml of culture.

Source: Pikalek and Necasek (1983).

TABLE 7-3. MUTAGENICITY EVALUATION OF NICKEL: GENE MUTATIONS IN YEAST AND CULTURED MAMMALIAN CELLS

Test System	Cell Line	Test Compound	Concentration	Reported Response	Comments	Reference
Saccharomyces cerevisiae	D7	Nickel sulfate	0.1 M	+ gene conversion + reverse mutation	Data are lacking. Only one concentration used, no dose-response.	Singh (1983)
Chinese hamster	V79	Nickel chloride	0.4 mM (5 μg/ml), 0.8 mM (10 μg/ml)	+ HGPRTase	At lower concentrations results are similar to controls. At higher concentrations the cell survival was too low to get a realistic estimation of mutation rate.	Miyaki et al. (1980)
Chinese hamster ovary cells	CHO	Nickel chloride	Not reported	+ HGPRTase	Data not reported.	Hsie et al. (1979)
Mouse lymphoma	L5178Y	Nickel chloride	40, 52, 71, 95, 127 μg/ml	+ TK Locus	Dose-response relationship was noted.	Amacher and Paillet (1980)

5.8 ± 0.8 per 10^6 survivors. The cell survival rate was 55 percent at 0.4 mM and 0.4 percent at 0.8 mM, respectively. At the higher survival rate (55 percent), the mutation frequency (7.1 ± 0.2 per 10^6 survivors) was almost similar to that of the control rate (5.8 ± 0.8 per 10^6 survivors). At the lower cell survival rate (0.4 percent) the concentration of nickel (0.8 mM) was too toxic to result in a realistic estimate of mutants. In the absence of data between concentrations of 0.4 mM and 0.8 mM, this report cannot be regarded as an indication of a positive mutagenic response of nickel chloride.

Hsie et al. (1979) studied the mutagenicity of nickel chloride in cultured Chinese hamster ovary cells, CHO, at the HGPRTase locus, using 6-thioguanine as another purine analog selective agent. According to these authors, nickel chloride was mutagenic. However, the authors did not provide data to support their conclusion. The authors indicated that the results were preliminary and needed further confirmation.

Amacher and Paillet (1980) reported that nickel chloride was mutagenic in mouse lymphoma L5178Y cells. Nickel chloride at concentrations of 1.69×10^{-4} M (40 μg/ml), 2.25×10^{-4} M (52 μg/ml), 3.00×10^{-4} M (71 μg/ml), 4×10^{-4} M (95 μg/ml), and 5.34×10^{-4} M (127 μg/ml) induced 0.95 ± 0.17, 1.00 ± 0.25, 0.88 ± 0.06, 1.00 ± 0.08, and 1.38 ± 0.24 trifluorothymidine-resistant mutants per 10^4 survivors. The cell survival at these concentrations ranged from 32 ± 2 to 22 ± 3 percent. These results demonstrate a dose-related response and translate into a 4- to 5-fold increase in the mutation frequency over the control level (0.38 ± 0.06). Cultures treated with one percent saline served as controls.

The studies of Miyaki et al. (1980) and Hsie et al. (1979) are lacking in data; the study of Amacher and Paillet (1980) is the only study that indicates that nickel is mutagenic in cultured mammalian cells. Confirmation of this study by independent investigators in other laboratories is desirable before concluding that nickel is mutagenic in cultured mammalian cells.

7.2. CHROMOSOMAL ABERRATION STUDIES

The ability of nickel compounds to induce chromosomal aberrations in cultured mammalian cells has been investigated, and these studies are summarized in Table 7-4. Additional studies on in vivo induction of chromosomal aberrations are summarized in Table 7-5.

TABLE 7-4. MUTAGENICITY EVALUATION OF NICKEL: IN VITRO CHROMOSOMAL ABERRATIONS

Indicator Cells	Duration of Treatment	Test Compound	Concentration	Reported Response	Comments	Reference
Mouse mammary carcinoma cells FM3A	24h, 48h	Nickel chloride, nickel acetate	1.0×10^{-3}M 6.4×10^{-4}M 3.2×10^{-4}M	-		Umeda and Nishimura (1979)
	48h	Potassium cyanonickelate, nickel sulfide	Same as above	+	Effects of potassium cyanonickelate may be due to cyanide moiety. No statistical analysis of data.	
Mouse mammary carcinoma cells FM3A	6, 24, 48h in the test compound, recovered in normal medium after 24, 48, 72, and 96h culture	Nickel chloride, nickel acetate, potassium cyanonickelate, nickel sulfide	1.0×10^{-3}M 6.4×10^{-4}M 3.2×10^{-4}M	+	Delayed effects. No statistical analysis of data.	Nishimura and Umeda (1979)
Human lymphocytes	48h	Nickel sulfate	1.9×10^{-5}M (5 μg/ml)	+	No dose-response.	Larramendy et al. (1981)
Syrian hamster embryo cells	24h	Nickel sulfate	1.9×10^{-5}M (5 μg/ml)	+	No statistical analysis.	

TABLE 7-5. MUTAGENICITY EVALUATION OF NICKEL: IN VIVO CHROMOSOMAL ABERRATIONS

Species	Cell Source	Test Compound	Dosage and Route	Treatment Duration	Response	Comments	Reference
Human	Lymphocytes (chromosomal aberrations)	Ni	0.5 mg Ni/m^3 (range 0.1-1.0 mg Ni/m^3)	7-29 years 45-57 years	-		Waksvik and Boysen (1982)
Rat	Bone marrow and spermatogonial cells	Nickel sulfate	3 and 6 mg/kg for 7 and 14 days	Subchronic	-	No data. No rationale for dosage selection.	Mathur et al. (1978)
Mouse	Bone marrow cells (micronucleus test)	Nickel chloride and nickel nitrate	25 mg/kg (50% LD50) 56 mg/kg (50% LD50) IP	30 hours 30 hours	-	Dose response not studied.	Deknudt and Leonard (1982)
Mouse	Dominant lethal test	Nickel chloride and nickel acetate	25 mg/kg (50% LD50) 56 mg/kg (50% LD50) IP	Acute	-	Dose response not studied. Not clastogenic but induced preimplantation failure.	Deknudt and Leonard (1982)
Mouse	Embryonic cells derived from treated male germ cells	Nickel nitrate	40 mg/kg 56 mg/kg	Acute	-	Not clastogenic but reduced fertilizing capacity of sperm.	Jacquet and Mayence (1982)

7.2.1 Chromosomal Aberrations In Vitro

Umeda and Nishimura (1979) exposed FM3A mammary carcinoma cells derived from C3H mice to various concentrations of nickel chloride, nickel acetate, potassium cyanonickelate, and nickel sulfide, and analyzed air-dried chromosomal preparations for aberrations. Nickel chloride and nickel acetate induced no aberrations at concentrations of 1.0×10^{-3}, 6.4×10^{-4}, and 3.2×10^{-4} M when cells were exposed for 24 and 48 hours. Potassium cyanonickelate at the same concentrations induced 4- to 18-fold increases in aberrations over the control value (2 percent) following 48 hours of treatment. Potassium cyanide, which was used as a positive control, induced aberrations similar to potassium cyanonickelate, indicating that the cyanide moiety may be responsible for aberration induction. The aberrations induced by the test compounds were mainly in the form of gaps. The same concentrations of nickel sulfide also induced many-fold (6 to 14) increases in aberrations over the control value (2 percent) at 48 hours of treatment. The concentration of 1.0×10^{-3}M was cytotoxic for all the test compounds. No statistical analysis was provided in this report.

Nishimura and Umeda (1979), in a continuation of their experiments described above, detected chromosomal aberrations in FM3A cells recovered in normal growth medium following exposures to nickel chloride, nickel acetate, potassium cyanonickelate, and nickel sulfide. These investigators exposed 1.0×10^{5} cells/ml to various concentrations of nickel compounds for 6, 24, or 48 hours, washed the cells with Hanks' balanced salt solution (HBSS), and reincubated the cells in the control growth medium for another 24, 48, 72, or 96 hours. Chromosome preparations were made at the end of each recovery period using the flame-drying method, and 100 metaphases for each interval were analyzed for chromosomal aberrations. Nickel acetate at a concentration of 1.0×10^{-3} M induced no chromosomal aberrations after 6 hours of treatment and 24, 48, and 72 hours of recovery. After 24 hours of treatment and reincubation periods of 24, 48, and 72 hours, the same concentration induced 5 to 10 percent aberrations (breaks, exchanges and fragments); after 48 hours of treatment and 24, 48, 72, and 96 hours of reincubation, no metaphases were noted. Nickel acetate at a concentration of 8×10^{-4} M after 48 hours of treatment induced 20 percent aberrations only after 48 hours of reincubation, after which aberrations were observed to the extent of 20 percent. At a concentration of 6×10^{-4} M, aberrations were also observed after 24 hours of reincubation. Nickel chloride, nickel sulfide, and potassium cyanonickelate induced similar clastogenic responses. The authors speculated that the nickel compounds induced damage to DNA in the cells but required periods of recovery for the cells to express the genetic damage in the form of chromosomal aberrations. This was probably due to a delay in cell cycle.

Larramendy et al. (1981) investigated the clastogenic effect of nickel sulfate in human lymphocyte cultures. Nickel sulfate (hydrated) at a concentration of 1.9×10^{-5} M (5.0 μg/ml) induced 14 aberrations in 125 metaphase cells (11.20 percent), or 0.07 ± 0.02 aberrations per metaphase following a 48-hour treatment. The background frequency was three aberrations in 200 metaphases (1.5 percent). The aberrations included gaps, chromatid breaks, and chromosome breaks, including rings and minutes. Nickel sulfate also induced 33 aberrations in 200 metaphases (16.5 percent) or 0.16 ± 0.03 aberrations per metaphase in Syrian hamster cells exposed to the same concentration (5.0 μg/ml) for 24 hours. The majority of the aberrations were of chromatid type. The aberrations in both these cell types were many-fold higher than the control values. Unfortunately, this study is limited because only one concentration was tested by these investigators.

Clearly, well designed in vitro chromosomal aberration studies using nickel compounds are necessary before concluding that nickel is clastogenic in cultured mammalian cells. Emphasis should be given to dose-response relationships and statistical analyses of the data.

7.2.2 Chromosomal Aberrations In Vivo

Mathur et al. (1978) failed to detect chromosomal aberrations in bone marrow and spermatogonial cells of albino rats treated with nickel sulfate. Male albino rats were intraperitoneally injected with 3 and 6 mg nickel sulfate/kg in saline daily for periods of 7 and 14 days. After a period of 45 hours rest, the animals were sacrificed and chromosome preparations were made from bone marrow and spermatogonial cells. Fifty metaphases per dose group were scored for chromosomal aberrations. Acccording to these authors, the number of aberrations in experimental animals was not significantly different from that of the control value. However, the authors did not provide data to support their conclusion. No rationale, such as LD_{50}, was provided for dosage selection.

Waksvik and Boysen (1982) analyzed blood lymphocytes for chromosomal abnormalities and sister chromatid exchanges from workers exposed to nickel in a refinery. Three groups of workers were studied. According to these investigators, the subjects were nonsmokers and nonalcohol users and did not use drugs regularly. The workers had not received any form of therapeutic irradiation. Of the three groups, two served as experimental and the third as control. In the experimental groups, the first group of 9 workers was exposed to a range of 0.1 to 1.0 mg Ni/m^3 (0.5 mg Ni/m^3) from 7 to 29 years, with an average of 21.2 years. The plasma concentration of nickel in blood ranged from 1 to 7 (µg/l). Cytogenetic analysis revealed an average of 11.9 percent chromosomal gaps and 0.9 percent chromosomal breaks compared to control frequencies of 3.7 percent gaps and 0.6 percent breaks. The average frequency of sister chromatid exchange per metaphase was 4.8 compared to the control level of 5.1. The second experimental group of 10 workers was exposed to an average nickel concentration of 0.2 mg/m^3 air, a range of 0.1 to 0.5 mg Ni/m^3. The age of the workers ranged from 45 to 57 years, with an average exposure period of 25.2 years. The average plasma concentration of nickel in these workers was 5.2 µg/l of blood. Chromosomal analysis revealed 18.3 percent gaps and 1.3 percent chromosomal breaks. This study is inconclusive because chromosomal gaps, which may restitute to normal chromosomes, do not represent true chromosomal aberrations, and the frequency of chromosomal breaks reported in the paper was not significantly different from the control value. Furthermore, these workers did not exhibit increased incidence of sister chromatid exchanges over the control level.

Deknudt and Leonard (1982) investigated the ability of nickel chloride and nickel nitrate to induce chromosomal aberrations using the micronucleus test and the dominant lethal assay in mice. Toxic dosage was determined to be 50 mg/kg for nickel chloride and 112 mg/kg for nickel nitrate.

In the micronucleus test, nickel chloride at a concentration of 25 mg/kg (50 percent LD$_{50}$) and nickel nitrate at a concentration of 56 mg/kg (50 percent LD$_{50}$) were used. One thousand polychromatic erythrocytes from bone marrow cells of five male mice were scored for each test compound. The yields of micronucleated cells were 2.60 ± 0.51 and 3.20 ± 0.58, respectively, for nickel chloride and nickel nitrate. These yields were well within the control level of 2.60 ± 0.24. Cyclophosphamide was used as a positive control.

In the dominant lethal test, male mice were intraperitoneally injected with 25 mg/kg of nickel chloride and 56 mg/kg of nickel nitrate. Treated males were bred with untreated females weekly for four weeks covering the entire spermatogenic cycle. Pregnant mice were sacrificed and the incidence of pre- and postimplantation losses in treated and control groups was recorded. Nickel salts did not increase the postimplantation loss significantly over the control level. However, these nickel compounds reduced the number of implantations, indicating the toxicity of the metal for the preimplantation zygotes. The authors indicated that since dominant lethals are generally a result of chromosomal aberrations induced in germ cells, the lack of dominant lethal effects in these experiments suggested that nickel was not clastogenic in male germ cells. Since only a single dose was tested in both of these studies, a positive result at other doses cannot be excluded.

Jacquet and Mayence (1982) studied the effects of nickel nitrate in male germ cells of mice using embryonic cell cultures (see Chapter 6 for discussion of study). The authors concluded that nickel nitrate induced toxicity in germ cells but did not induce chromosomal aberrations as evidenced by reduced numbers of viable embryos, but normal development in those that were viable.

The above chromosomal aberration studies suggest a lack of clastogenic activity of nickel in _in vivo_ systems. However, some of these studies have also indicated that nickel is toxic to male germ cells, resulting in reduced numbers of fertilized eggs. Studies on the effects of nickel have not been performed in female germ cells. This is important because many metals, such as cadmium and mercury, have been found to induce chromosomal nondisjunction leading to aneuploidy in female germ cells of mammals (Watanabe et al., 1979; Mailhes, 1983). Consequently, studies on the effects of nickel in female mammalian germ cells and additional studies in male germ cells are needed before concluding that nickel is not a germ cell mutagen. Nickel should also be tested for its ability to cause nondisjunction in somatic cells.

7.3 SISTER CHROMATID EXCHANGE (SCE) STUDIES _IN VITRO_

Nickel compounds have been tested for the induction of SCE in a variety of _in vitro_ systems (Table 7-6).

Wulf (1980) investigated SCE in human lymphocytes exposed to nickel sulfate for 72 hours at various concentrations. There was a dose-related increase in SCE. At a concentration of 2.33×10^{-4}M/l (55 μg/ml), the SCE frequency was 9.5 ± 0.84 per metaphase ($p < 0.0005$); at a concentration of 2.33×10^{-5}M/l (5.5 μg/ml), the SCE frequency was 8.50 ± 0.51 per metaphase ($p < 0.0025$); and at a concentration of 2.33×10^{-6}M/l (0.55 μg/ml), the SCE frequency was 7.24 ± 0.38

TABLE 7-6. MUTAGENICITY EVALUATION OF NICKEL: IN VITRO SISTER CHROMATID EXCHANGES

Sources of Cell Culture	Duration of Cultures	Test Compound	Concentration	Treatment Time	Reported Response	Comments	Reference
Human lymphocytes	72h	Nickel sulfate	2.33×10^{-4} mol/l 2.33×10^{-5} mol/l 2.33×10^{-6} mol/l	72h	+	Dose response reported with student t-test.	Wulf (1980)
Chinese hamster Don cells	72h	Nickel sulfate Nickel chloride	50 µg/ml 32 µg/ml	72h	+	No dose response studied. Data analyzed statistically.	Ohno et al. (1982)
Human lymphocytes		Nickel sulfide	Not reported	Not reported	+	No data were presented.	Anderson (1983)
Human lymphocytes	Not reported	Nickel sulfide		24h, 48h	+	No dose response.	Saxholm et al. (1981)
Human lymphocytes	64h	Nickelous chloride	1.0×10^{-6} M 9.88×10^{-6} M 5.45×10^{-5} M 1.19×10^{-4} M	64h	+	Data analyzed with a student t-test.	Newman et al. (1982)
Human lymphocytes	72h	Nickel sulfate	9.5×10^{-6} M (2.5 µg/ml), 1.9×10^{-5} M (5 µg/ml)	24h, 48h	+	Low concentration used. The results would probably be more dramatic at higher concentration.	Larramendy et al. (1981)
Syrian hamster cells	72h	Nickel sulfate	3.8×10^{-6} M (1 µg/ml), 9.5×10^{-6} M (2.5 µg/ml), 1.9×10^{-5} M (5 µg/ml)	24h, 48h	+		

per metaphase ($p < 0.05$), compared to the control frequency of 6.24 ± 0.42 SCE per metaphase. The study was well conducted and the data were statistically analyzed (student t-test).

Ohno et al. (1982) investigated the induction of SCE by nickel sulfate and nickel chloride in the Chinese hamster Don cells. These authors determined the $TCID_{50}$ (50 percent inhibition dose of tissue culture cells) as 50 μg/ml for nickel sulfate and 32 μg/ml for nickel chloride. Nickel sulfate and nickel chloride at these concentrations resulted in 7.2 and 6.2 SCE/cell, respectively. The spontaneous SCE level was 3.90 ± 0.82/cell. The authors indicated that these results were statistically significant at the 95 percent confidence limit compared to the spontaneous level ($p < 0.05$). Although no attempts were made to study the dose response, the statistical analysis of the data supports the fact that nickel induces SCEs in Chinese hamster cell cultures.

In a preliminary SCE study, Anderson (1983) noted a weak mutagenic effect of nickel sulfate on lymphocytes of one human donor without apparent dose-response relationship and no effect of nickel on lymphocytes of another human donor. Data were not presented in this report.

Saxholm et al. (1981) investigated the ability of nickel subsulfide to induce SCE in human lymphocytes. Lymphocyte cultures were treated at a concentration range of 1 to 100 μg/ml for 24 hours and 48 hours, and analysis of chromosomes for SCEs was performed. In the 24-hour treatment group, the SCE frequency was similar to that of the control group, whereas in the 48-hour treatment group the results were significantly higher than controls (t-test, $p < 0.001$). The toxic concentration level was 1000 μg/ml, and there was no dose-related response in the increase of SCE frequencies.

Newman et al. (1982) detected a significant increase in the incidence of SCEs over background in human lymphocytes exposed to nickelous chloride. At a concentration of 1.19×10^{-4}M (28 μg/ml), nickel approximately doubled the baseline SCE incidence to yield a mean value of 8.52 ± 0.33 SCEs per cell. Control cells produced a mean background incidence of 3.92 ± 0.7 SCEs per cell. Nickel concentrations lower than 1×10^{-4}M yielded mean SCE values between 8.52 and the control value of 3.92 ± 0.7 exchanges per cell. Concentrations of nickel at or above 5×10^{-4}M were toxic to lymphocytes. Data were analyzed with a student t-test.

Larramendy et al. (1981) investigated the effect of nickel sulfate on SCE frequencies in human lymphocytes. Nickel sulfate at concentrations of 9.5 x

10^{-6}M (2.5 μg/ml) and 1.9 x 10^{-5}M (5.0 μg/ml) induced 17.20 ± 0.90 and 18.95 ± 1.52 SCEs per cell, respectively. The control value was 11.30 ± .60 SCE per cell. The range of SCE per cell in control cultures was 5 to 18 and 7 to 20 in human and hamster samples, respectively. In the metal-treated samples the SCE range was from 10 to 35.

In Syrian hamster cells exposed to 3.8 x 10^{-6}M (1 μg/ml), 9.5 x 10^{-6}M (2.5 μg/ml), and 1.9 x 10^{-5}M (5.0 μg/ml), nickel sulfate induced 15.95 ± 0.92, 17.25 ± 1.44, and 21.25 ± 1.13 SCEs, respectively. The background level of SCEs in control cultures was 11.55 ± 0.84 per metaphase. The authors claimed that the increases in SCE were dose-related. Toxic doses and cell survival data were not indicated in this paper. The rationale for dosage selection was given on the basis of morphologic cell transformation. Compared to other studies on SCE induction, this study employed relatively lower concentrations of the test compound.

The weight of evidence, based on the above studies, demonstrates that nickel compounds (nickel sulfate, nickel subsulfide, and nickel chloride) induce SCEs in cultured mammalian cells and cultured human lymphocytes. However, in the only in vivo study reported (Waksvik and Boysen, 1982) where workers were exposed to nickel in a refinery, a negative response for SCE in lymphocytes was noted (see Section 7.2.2).

7.4 OTHER STUDIES INDICATIVE OF MUTAGENIC DAMAGE

7.4.1 Rec Assay in Bacteria

Nishioka (1975) and Kanematsu et al. (1980) found nickel monoxide and nickel trioxide to be nonmutagenic in the rec assay, which measures inhibition of growth in *Bacillus subtilis*.

Kanematsu et al. (1980) exposed *Bacillus subtilis* strains H17 (rec+) and M75 (rec-) to 0.05 ml of 0.005 to 0.5 M nickel monoxide and nickel trioxide in agar petri plates. The treated plates were first cold incubated (4°C) for 24 hours and then incubated at 37°C overnight. Inhibition of growth due to DNA damage was measured in both the wild type H17 (rec+) and the sensitive type (rec-) strains. The difference in growth inhibition between the wild-type strain and the sensitive strain was less than 4 mm, which was considered to be indicative of a negative response.

Nishioka (1975) detected no rec effect in Bacillus subtilis using nickel chloride.

7.4.2 S-Phase-Specific Cell Cycle Block

Costa et al. (1982a) investigated the ability of water-insoluble nickel, crystalline nickel subsulfide (Ni_3S_2), crystalline nickel monosulfide (NiS), crystalline nickel selenate (Ni_3Se_2), and crystalline nickel oxide (NiO) to induce cell cycle block in Chinese hamster ovary (CHO) cells, using the flow cytometric technique. All these compounds induced S-phase-specific cell cycle block. At higher concentrations, nickel subsulfide (10 μg/ml) and nickel selenate (5 μg/ml) also caused accumulation of cells in mitosis. This appears to indicate that nickel subsulfide and nickel selenate, in addition to blocking cells in the S-phase, also inhibit mitosis.

7.4.3 Mammalian Cell Transformation Assay

Sunderman (1983) has published an extensive review of morphologic cell transformation induced by nickel compounds.

DiPaolo and Casto (1979) evaluated nickel along with 44 other metals for its ability to induce morphologic transformation in Syrian hamster embryo cells in vitro. Nickel subsulfide (Ni_3S_2) induced a positive response in these studies, whereas amorphous nickel monosulfide gave negative results in the transformation assay.

DiPaolo and Casto (1979) also found that when divalent nickel was administered to pregnant Syrian hamsters on day 11 of gestation, morphologic transformation was observed in cell cultures derived from 13-day-old embryos. Costa et al. (1979) showed that morphologic transformation induced by nickel subsulfide in Syrian hamster embryo cells was dose-dependent. These transformed cells induced fibrosarcomas when implanted subcutaneously into "nude" mice. Costa et al. (1982b) found that soluble nickel chloride ($NiCl_2$) induced morphologic transformation of Syrian hamster embryo cells. Saxholm et al. (1981) found that nickel subsulfide (Ni_3S_2) induced morphologic transformation in C3H/10T1/2 cells. Hansen and Stern (1982) studied the activity of nickel dust, nickel subsulfide, nickel trioxide (Ni_2O_3), nickel oxide (NiO), and $Ni(C_2H_3O_2)_2$ for in vitro transformation of Syrian hamster BHK-21 cells. These compounds varied in their potency to transform the cells but produced the same number of transformed colonies at the same degree of toxicity (50 percent survival).

The synergistic effects of nickel compounds with benzo(a)pyrene (BP) to induce morphologic transformation in Syrian hamster embryo cells were studied by Costa and Mollenhauer (1980) and Rivedal and Sanner (1981, 1980). Costa and Mollenhauer found that pretreatment of cells with BP enhances cellular uptake of nickel subsulfide particles. Rivedal and Sanner found that a combined treatment of nickel sulfate and BP results in a transformation frequency of 10.7 percent, compared to 0.5 percent and 0.6 percent for the individual substances.

Nickel-induced morphologic cell transformation may be due to somatic mutations, because there is suggestive evidence of nickel-induced gene mutations (Amacher and Paillet, 1980) and chromosomal aberrations (Larramendy et al., 1981) in cultured mammalian cells.

7.4.4 Biochemical Genotoxicity

Sunderman (1983) reviewed the biochemical genotoxicity of nickel compounds. Sigee and Kearns (1982) demonstrated that nickel in the chromatin of dinoflagellates associated with high-molecular-weight proteins and nucleic acids. Kovacs and Darvas (1982) demonstrated the localization of nickel in centrioles of HeLa cell cultures. Hui and Sunderman (1980) found 0.2 to 2.2 mol ^{63}Ni/mol of DNA nucleotides in DNA isolated from liver and kidney of rats treated with $^{63}NiCl_2$ or $^{63}Ni(CO)_4$. Ciccarelli and Wetterhahn (1983) demonstrated nickel-nucleic acid-histone complexes in liver and kidney of nickel carbonate-treated rats. They proposed that nickel may initiate DNA damage by forming a covalent nickel-DNA complex.

Ciccarelli and Watterhahn (1982) demonstrated DNA-protein crosslinks and DNA strand breaks in kidney cells of rats exposed to nickel carbonate. In Chinese hamster ovary cells, crystalline nickel monosulfide was found to induce DNA strand breaks (Robinson and Costa, 1982). However, DNA strand breaks should not be accepted as the principal evidence of direct DNA damage by metal compounds, since strand breaks can also be produced by indirect, nonspecific effects, such as intracellular release of lysosomal nucleases (Levis and Bianchi, 1982).

Zakour et al. (1981) studied the effect of nickel in the DNA infidelity assay and found that cations of nickel increase misincorporation of nucleotide bases in the daughter strand of DNA that is synthesized *in vitro* from synthetic polynucleotide templates by microbial polymerases.

The effects of nickel cations on transcription of calf thymus DNA and phage t_4 DNA by RNA polymerase from *E. coli* B were studied by Niyogi and Feldman (1981) under carefully controlled conditions. These studies demonstrated that nickel ion concentrations which inhibited overall transcription increased RNA chain initiation.

The studies cited demonstrate that nickel compounds induce genotoxic effects. The translation of these effects into actual mutations, however, is still not clearly understood.

7.5 REFERENCES

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8. CARCINOGENIC EFFECTS OF NICKEL

A large number of experimental, clinical, and epidemiologic studies have been conducted over the years to determine the role of various nickel compounds in occupational and experimental carcinogenesis. These studies have been the subject of a number of reviews (Mastromatteo, 1983; Sunderman, 1981; Wong et al., 1983; National Institute for Occupational Safety and Health, 1977a, 1977b; International Agency for Research on Cancer, 1972, 1976, 1979; National Academy of Sciences, 1975).

8.1 EPIDEMIOLOGIC STUDIES

The epidemiologic evidence on nickel carcinogenesis in humans, with particular regard to specific nickel species, is reviewed in this section. The epidemiologic studies reviewed are organized on the basis of the worksites involved. The study designs, results, and conclusions are summarized and critiqued. An attempt is made to delineate the actual nickel exposures that occurred at each worksite as the result of the processes in use at that worksite during the time periods studied, based on information contained in the reports reviewed.

8.1.1 Clydach Nickel Refinery (Clydach, Wales)

The Clydach Nickel Refinery opened in 1902 in the County Borough of Swansea, South Wales, Britain. A Bessemer matte from Canada was refined at Clydach by the carbonyl process, and a number of changes in the production process have been made since the plant was opened. The first epidemiologic investigation of cancer risk at the Clydach plant was reported in 1939 (Hill, 1939, unpublished). This was followed by a series of studies between 1958 and 1984.

Morgan (1958) has provided the most detailed description of the production process and related exposures at the Clydach plant. There were essentially six steps in the refining of nickel at Clydach: (1) crushing and grinding of the matte; (2) calcination (oxidation by heating) of the matte, resulting in the production of mixed oxides of copper and nickel; (3) copper extraction of the matte using sulfuric acid; (4) reduction of the nickel oxides to produce impure nickel powder; (5) volatilization of the reduced nickel using carbon monoxide gas to produce nickel carbonyl; and (6) decomposition, in which the nickel carbonyl is precipitated onto nickel pellets to form pure nickel, releasing carbon monoxide in the process.

Arsenic was a contaminant of the sulfuric acid used to remove copper from the matte. The amount of arsenic in the acid peaked between 1917 and 1919 and declined significantly after 1921. In 1924, all of the remaining "old stock" of acid which contained arsenic was used. Since 1926, the acid was practically free of arsenic.

After the decomposition step, the residue was sent to a concentration plant where it was calcined and copper and nickel were extracted using sulfuric acid. This resulted in a matte which had a relatively high concentration of precious metals. In the reduction and volatilization process and the decomposition step, the matte had a very low concentration of copper due to prior extraction with sulfuric acid.

The following changes occurred between 1902 and 1957 with regard to worker exposures. The use of sulfuric acid with a high concentration of arsenic was discontinued after 1924. A plow type of calciner was employed from 1902 to 1911. It was changed to "double deckers with rotary rakes in 1910 which, although very dusty, constituted an improvement over the first type" (in terms of decreasing exposure) (Morgan, 1958). In 1922, cotton nose and mouth respirator pads were issued; in 1924, calciners were shortened and improved, although it was not stated how the improvements affected exposure; in 1929, the copper sulfate plant was closed down; in 1934, the composition of the matte was changed to include only 2 percent copper as compared to 35 percent and 2 percent sulfur compared to 20 percent; in 1935, electrostatic precipitators were added which diminished the amount of dust emitted from the stacks. In addition, the crushing and grinding operations were centralized in a single plant. The author noted that the plant was "virtually dust free" (Morgan, 1958). Prior to this time, crushing and grinding had been done separately, and the operations were characterized as "very dusty." In 1936, new calciners were installed. The old type had led to underground flues which needed frequent cleaning. The author stated, "It is significant that most of the nasal cancers occurred amongst men who were engaged in cleaning those flues. The new calciners are in well-ventilated rooms and the flue gases from these calciners are taken to two large electrostatic precipitators" (Morgan, 1958).

The exposures to nickel species and other substances varied according to the type of work performed and by calendar time at the Clydach plant. In addition, since the residue from the carbonylation extraction was passed through the complete refining process several times, the concentrations of other metals, such as cobalt, selenium, and precious metals, increased. Table 8-1 provides some descriptive information on exposures associated with different work areas (Morgan, 1958; INCO, 1976).

Five different populations at risk (PAR) from the Clydach plant are described in the seven reports which were issued between 1939 and 1983 and that are reviewed here. Hill (1939) defined an approximate PAR employed at the plant from 1929 to 1938 in order to obtain a rough estimate of the standardized mortality ratio (SMR) for lung and nasal cancer. The analysis is presented as a cohort investigation, but is more likely a proportionate mortality ratio (PMR) study. Hill's investigation is described by Morgan (1958) in some detail. In addition, Morgan also provides the only complete description of the cohort and total PAR from the Clydach plant. Between 1902 and 1957, there were 9,340 "new entrants" to the plant. Morgan (1958) identified 2,094 who worked at least one year. His study gives important background information which is useful in interpreting reports issued between 1970 and 1984. A third PAR was defined by Doll (1958), who published a PMR study of lung and nasal cancer occurring in four "local authority districts" in South Wales. The study was initiated to investigate risks in the nickel industry, which by definition in South Wales was the Clydach plant.

The fourth PAR is a less definitive subset of the cohort described by Morgan (1958). It includes those likely to have been employed at least five years between 1902 and 1944, and who were employed as of 1939 (1934 in two reports). The definition of this PAR, with regard to exposure and calendar time of employment, must be given careful consideration when interpreting the risk estimates.

A fifth PAR was described by Cuckle et al. (1980), who studied workers in the Wet Treatment Plant and the Chemical Products Department. Details on each of the PARs, results, and methodologic issues pertaining to the interpretation of results are discussed below.

TABLE 8-1. EXPOSURES BY WORK AREA (CLYDACH, WALES)

Work area	Exposures	Level	Changes
Crushing, grinding, and calcining shed	Dust, nickel, oxides, SO_2, copper, sulfur	Very high	Greatly reduced after 1930 from separation of crushing and grinding operations and improvements in production.
Copper extraction	Copper sulfate, arsenic (contaminant)	+?	The arsenic levels in the sulfuric acid used for copper extraction peaked between 1917 and 1919. The levels declined dramatically after 1921. Since 1926, the acid was practically free of arsenic.
Reduction, volatilization,	Nickel powder, nickel carbonyl, CO decomposition	?	

8.1.1.1 Hill (1939, unpublished). This was the first epidemiologic study of the Clydach plant workers, and was summarized by Morgan (1958). The study is noteworthy because it identifies the risks associated with the nickel refinery. It provides no risk estimates by species of nickel.

The population at risk was not defined per se, but the age distribution and number of employees over time was estimated from pension records and employee lists for two different dates, 1931 and 1937. Sixteen lung and 11 nasal cancer deaths were identified, but the follow-up method was not described and it is not known exactly how the deaths corresponded to the PAR. Nonetheless, measures of risk were derived by applying age-specific death rates for England and Wales to the age-specific groups of the "approximate" PAR. The observed-to-expected ratio was 16 (16/1) for lung cancer and greater than 11 (11/<1) for nasal cancer. The excess lung and nasal sinus cancer deaths were almost exclusive to process workers; no nasal cancer deaths occurred among nonprocess workers.

This study documents the fact of excess risks in the nickel refining plant at Clydach. The PAR was not well defined, nor was the identification of deaths well described. The risks for lung and nasal sinus cancer among process workers were very high, and it is unlikely that they were spurious.

8.1.1.2 Morgan (1958). This was a study of workers employed at least one year at the Clydach refinery between 1902 and 1957. The paper provides the only detailed description of the total cohort entering the plant, and the most complete description of the nickel refining process and changes in the plant over its 55 years of operation.

No analysis of risks was presented. Descriptive statistics were reported on the number of employees and the number of deaths from lung and nasal sinus cancer by calendar period of first employment, length of employment, and department. The investigation suffers from a lack of detail on the method of follow-up. The report contains detailed reference information on the occurrence of deaths, the size of the cohort, and possible risks by calendar time and department. It does not appear that this data set has been fully exploited, since information on the jobs held and length of employment appear to be available on all employees.

The total number of new entrants into the plant between 1902 and 1957 was 9,340. The company had a pension plan involving annual visits which enabled it to keep records of all pensioners wherever their place of residence. The author did not state, however, how many years one had to work to be eligible for a pension. When a pensioner died, it was necessary for dependents to furnish a death certificate in order to obtain death benefits. The cause of death was therefore recorded in every case.

Exposure was defined in terms of category of work or process, and in terms of total length of employment. These factors were considered independently, and no measure of exposure which incorporated both department or type of process and length of employment was provided.

The report provides information on the number of workers and cases of lung cancer by year of entry and number of years of service. Out of approximately 2,100 workers entering the plant between 1902 and 1929, 1,240 worked 1 to 10 years, 79 worked 11 to 20 years, and 780 worked over 20 years. Fifty-three employees entered the plant between 1900 and 1904, 178 between 1905 and 1909, 269 between 1910 and 1914, 667 between 1915 and 1919, 602 between 1920 and 1924, and 326 between 1925 and 1929. Table 8-2 shows the percentage of workers diagnosed with nasal or lung cancer by year of entry and length of employment. The risk of nasal cancer appears to have been highest for those first employed between 1905 and 1914. The rate of nasal cancer among those first employed between 1900 and 1904 is low in comparison with other periods. However, only 53 employees worked more than one year and were first employed during this time period. The pattern for lung cancer is somewhat different than that for nasal cancer by year of entry and length of employment. Workers starting between 1900 and 1904 had a rate similar to those first employed between 1905 and 1914. Individuals entering between 1900 and 1904 and working less than ten years had the highest rate, 20 percent, as compared to those entering during other periods and working less than ten years. All subsequent cohorts, defined by year of entry and working for one to ten years, had a lung cancer rate of close to zero. The rates for both nasal and lung cancer were high for those first employed between 1900 and 1924. The risk for both types of cancer dropped dramatically among those first employed between 1925 and 1929.

The study shows the distribution of cases of lung and nasal cancer by department or process. The calcination and copper sulfate departments appear to have had the highest risks of lung cancer of the eight departments listed. The rate of nasal cancer was highest in the calcination department (14/58), followed by the furnace (5/36) and copper sulfate (8/87) processes. However, it is difficult to interpret these rates, since the denominator is not clearly defined. To estimate rates, an average annual population size was derived, but the means used to derive this average are not clear. It could be an average number of person-years or an average number of persons.

8.1.1.3 Doll (1958). This was a community-based study of four local authority areas in South Wales, in which nickel industry workers, i.e., Clydach plant employees, were compared to workers in other occupations, excluding steel industry workers, coal miners, and selected industrial occupations such as oil refinery workers, aluminum workers, and copper smelter workers.

Cases were identified from death records, and were divided into three groups: lung cancer, nasal cancer, and all other causes of death. Between 1938 and 1956, 48 lung cancer cases and 13 nasal cancer cases were identified and categorized by the occupation listed on the death certificate. Analyses were presented for nickel industry workers as a whole, compared to all other

TABLE 8-2. PERCENT OF LUNG AND NASAL CANCER DEATHS AMONG WORKERS BY YEAR OF ENTRY AND LENGTH OF EMPLOYMENT (CLYDACH, WALES)

Year of entry	Length of employment	Percent of workers	
		Nasal	Lung
1900-1904	1-10	-	20
	11-20	-	14
	20+	2	15
1905-1909	1-10	0	0
	11-20	100	16
	20+	9	23
1910-1914	1-10	2	0
	11-20	28	22
	20+	19	21
1915-1919	1-10	0	0-2
	11-20	13	20
	20+	4	6
1920-1924	1-10	1	1
	11-20	5	21
	20+	2	13
1925-1929	1-10	0	0.5
	11-20	0	0
	20+	0	0

Source: Adapted from Morgan (1958).

occupations, and process and nonprocess nickel workers compared to all other occupations.

Analysis by calendar time in two of the local authority areas showed a decline in the PMR for lung cancer from 1,379 for the period 1938 to 1947 to 666 for the period 1948 to 1956. The author suggests that the decline in the PMR between these two periods does not necessarily reflect a decline in the risk of lung cancer among nickel workers. He suggested that the decline can, in part, be accounted for by a dramatic rise in the national lung cancer rate, which was due largely to the increased prevalence of smoking. The excess lung cancer risk, i.e., the difference between the observed and expected risk, for the two time periods noted above is constant, supporting the idea of no declining risk in the industry. The PMR overall for nasal cancer was extremely high, ranging from 19,600 to 24,200, depending upon the local areas which were included and the time period of coverage. The PMR for lung and nasal cancer was higher for process (defined as "processman" or "process worker" on the death certificate) versus nonprocess workers. The lung cancer PMR for process workers was 700 versus 340 for nonprocess workers. The nasal cancer PMR was 30,000 for process workers versus 12,000 for nonprocess workers.

8.1.1.4 Doll et al. (1970). This is the first of a series of three papers on the mortality risks among a select group of Clydach plant workers. The definition of the cohort was different from that used by Morgan (1958), who described the complete cohort, i.e., all workers entering the plant up to 1958. The cohort studied by Doll et al. was defined as men "likely" to have been employed for at least five years, who started between 1902 and 1944, and who were alive and employed as of April, 1934. Workers listed on at least two consecutive paysheets five years apart, i.e., April of 1934, 1939, 1944, and 1949, were included in the cohort. Given this definition, workers first employed before 1934 must have been employed longer than five years to meet the cohort criteria. For example, a worker who started in 1924 must have been employed 15 years to be included in the cohort, since, by definition, he was working in April of 1939. Length of employment and extent of exposure were thus highly correlated with year of first employment, and therefore any inference regarding risks by calendar time of first employment is necessarily confounded by length of employment.

Of a total of 845 men who met the cohort criteria, 563 began their employment before 1925, 77 between 1925 and 1929, and the remaining 205 during or after 1930. The follow-up period was 28 years, from 1939 to 1967, during which 113 lung and 39 nasal cancer cases were identified. Twenty-seven workers were lost to follow-up. Analyses were presented by age at first exposure, calendar time of first exposure, and calendar time of observation. Expected values for the analysis by time of first exposure were based on general population rates from England and South Wales, while values for the analysis by age of first exposure and calendar time of observation were based on an internal reference group.

The report noted the observed to expected values by year of first employment for nasal cancer, lung cancer, other neoplasms, and all other causes of death. All 39 nasal sinus cancer cases occurred among those starting employment before 1925. The overall SMR was 364 for workers starting before 1925, and ranged from a low of 116 among those starting between 1920 and 1924, to a high of 870 for those starting between 1910 and 1914. The SMR for workers starting before 1910 or after 1914, although still extremely high, was less than half that for the group starting between 1910 and 1914.

Only eight of the 113 lung cancer cases occurred among those starting employment on or after 1925. The SMR for workers starting before 1925 was 750. The SMR for those starting before 1915 ranged from 950 to 1,005 and dropped to 570 to 630 among workers entering during or after 1915. This trend may have been somewhat confounded by length of employment, since workers starting before 1915 were probably employed for longer periods of time than those starting during or after 1925.

The overall SMR for lung cancer for those starting during or after 1925 was 130, which was considerably less than the SMR for those starting before 1925. However, the length of the follow-up period was not as long for workers starting after 1924. In addition, because of the way the cohort was defined, the average length of employment was not as long for workers starting after 1924. The analysis by age at first exposure, which is limited to workers starting before 1925, shows a direct relationship between the risk of nasal cancer and the age at first exposure. In contrast, and except for the youngest age group, i.e., less than 20 years of age, there was a slight inverse relationship between the risk of lung cancer and age at first exposure.

Analyses in the Doll et al. (1970) study were also presented by calendar time of observation. The statistics given are difficult to interpret because of the long interval during which subjects entered the cohort, i.e., 1902 to 1924. Nonetheless, the risk for nasal cancer appears to have declined with time since exposure, or, as the authors state, "after the disappearance of the carcinogen after 1924."

In this study, the risk for lung cancer is clearly seen to have declined with calendar time. Again, however, the interpretation could have been more straightforward if the analysis had been carried out by time since first exposure. The authors suggested that the pattern of risk for lung cancer and age at first exposure may have been due to the differences in smoking patterns among different cohorts. In essence, even if the risk of lung cancer from nickel exposure were constant over time, the attributable risk for lung cancer from nickel exposure would decline with time because of a higher risk due to the increasing prevalence of smoking. This constitutes a plausible explanation for the pattern noted in the Doll et al. (1970) study (which assumes an additive effect for nickel and smoking).

The virtual absence of nasal cancer among those starting employment during or after 1925, and the dramatic decline in the risk of lung cancer for those starting during or after 1925, suggest that significant changes in exposure to various species of nickel and possibly other substances, such as arsenic, may account for these declines. In addition, the significantly elevated SMR for nasal cancer noted among those workers starting between 1910 and 1914 suggests that some change may have occurred during that time. Some notable process changes are: (1) before 1932, the partially refined ore imported from Canada contained a high proportion of copper and sulfur, as well as precious metals, in the nickel sulfide matte. After that time, the copper and sulfur content of the ore from Canada was significantly reduced. (2) In 1924, a new type of calciner was used, and sometime between 1922 and 1924, cotton respirators were introduced. These may have reduced exposures to larger particles, which would normally deposit in the nasal sinus area. (3) The level of arsenic in the sulfuric acid used to leach copper from the nickel matte reached a peak between 1917 and 1919, and declined dramatically after 1921. These changes, however, are not seen as having any direct correspondence to the changes in lung cancer risk.

8.1.1.5 Doll et al. (1977). This is an update of the study reported in 1970 by Doll et al. The follow-up period was extended to 37 years, from 1934 to 1971. The definition of the cohort was changed slightly to include all men likely to have worked at least five years as of 1929 or later. This change increased the number of workers meeting the cohort criteria who entered the plant before 1925 and decreased the overall average length of employment for this group. However, the group starting before 1925 was still highly selected in that it was composed of workers employed for more than five years.

Nine hundred thirty-seven workers met the cohort criteria, in contrast to 845 in the previous report. Thirty-seven were lost to follow-up, and 145 lung cancer and 56 nasal cancer cases were identified. A slightly larger proportion of the cohort started their employment before 1925 (68 percent versus 66 percent) due to the change in the cohort definition between this and the 1970 report (Doll et al., 1970).

Expected values for lung and nasal cancer were derived by applying age- and time-specific rates for England and Wales to the number of person-years of follow-up. Extremely high risks were reported for nasal sinus cancer. Even with the extended follow-up to 1971, no new cases of nasal cancer were identified among those workers who started employment after 1924. The nasal cancer SMRs by starting date were: 38,900 (<1910); 64,900 (1910 to 1914); 44,000 (1915 to 1919); and 9,900 (1920 to 1924). The peak SMR was among workers starting between 1910 to 1914. However, the difference between the 1910 to 1914 cohort and other groups defined by start date was not as great as was noted in the 1970 report by Doll et al. The change may in part be due to the revised cohort definition.

The magnitude of SMRs and the pattern for lung cancer by start date were essentially the same as that reported in 1970, with one exception. The SMR for those first employed between 1925 and 1929 was 250, higher than that reported in 1970 (Doll et al., 1970).

The authors suggested that the use of respirators, which were introduced in 1922 or 1923, could account for the virtual absence of nasal sinus cancer among workers starting employment after 1924. It would be of interest to know the extent of respirator use, and whether respirators were used throughout the plant or only in selected departments. Such documentation could provide valuable information on species-specific risks.

8.1.1.6 Cuckle et al. (1980, unpublished). This was a cohort study of 297 men who had been employed for at least 12 months between 1937 and 1960 in the Wet Treatment Department (WTD) or Chemical Products Department (CPD) of the Clydach plant. The WTD and CPD opened between 1937 and 1939. None of the cohort were employed at the Clydach plant prior to 1933, when, according to the authors, the lung and nasal cancer hazards were "eliminated." Follow-up was from 1938 to 1980, during which 13 deaths from lung cancer, 13 deaths from other cancers, and 79 deaths from other causes occurred. No deaths due to nasal sinus or laryngeal cancer were identified. Four subjects were lost to follow-up.

Feed material for the WTD originated in the nickel carbonyl extraction plant and was very high in nickel content, relatively low in copper and sulfur, and high in precious metals. Products from the WTD operation included ferric hydroxide, cobaltic hydroxide, precious metal residues, and copper sulfate and nickel sulfate crystals. The CPD, built in 1939, manufactured compounds and salts of nickel, cobalt, and selenium. The raw materials used included nickel oxide and black cobalt oxide from Canada, nickel sulfate and cobaltic hydroxide from the WTD, nickel powder and metal, cobalt metal, and selenium, as well as a range of acids and alkalies. The end products included, in addition to a number of other substances, salts and hydrates of nickel and cobalt, nickel cyanide, and cobalt ammonium sulfate.

Personal sampling values of total airborne nickel were obtained from the WTD and CPD for the period 1974 to 1978. These data showed that the nickel levels for the mean, median, and maximum were two to three times higher in the WTD than in the CPD. It should be noted, however, that these measurements were made 35 years after the plant opened, and may not be relevant to the exposures incurred earlier in the plant's history.

SMRs were calculated by multiplying age- and time-specific mortality rates for England and Wales by the age- and time-specific distribution of person-years for the study cohort. The SMR was highest for those with less than 20 years since first exposure (SMR = 178), as compared to an SMR of 107 for those with more than 20 years' exposure. Overall, those employed for 6 years or more in the plant had lower risks (SMR = 128 versus 142). The authors indicate that the workers who were employed only in the WTD and the CPD had the highest risk of lung cancer, with an SMR equal to 207, as compared to those who spent $\geqq$ 1 year of their working time in other departments.

Overall, this study showed low risks for lung cancer, a small number of cases, and very complex exposure circumstances. Given these factors, and the virtual absence of nasal sinus cancers in the cohort, this study is noteworthy for its contrast to other studies with cohorts of similar size. It should be kept in mind, however, that for the Clydach Plant during this period, the relative risks for lung cancer were declining and approaching unity, and that no nasal cancer cases were identified among workers whose employment began after 1924. The patterns noted in the WPD and the CPD are thus consistent with the pattern of risk for the plant overall.

8.1.1.7 Peto et al. (1984). This was the third of three papers reporting on the mortality risks among selected Clydach plant workers. Peto et al. provide the most extensive analysis to date, using regression methods to adjust for the possible confounding variables noted earlier. In addition, detailed employment records were compiled to improve the precision of studying risks by duration of employment in different work settings. The risks of cancer of the larynx, kidney, prostate, and stomach, as well as circulatory and respiratory disease, were investigated, in addition to cancer of the lung and nasal sinus. The definition of the cohort remained the same as that reported in Doll et al., 1977; however, follow-up was extended to 1981. There were 968 workers in the cohort, 18 of which were lost to follow-up--a decline from the 37 that had been reported in 1977 as being lost to follow-up. One hundred fifty-nine lung cancer and 58 nasal sinus cancer cases were identified. Much of the analysis was restricted to workers first employed before 1925. Both external (England and Wales) and internal comparisons were used. Exposure groups were defined by occupation and, in a separate analysis, by length of employment in the furnace and copper sulfate areas.

Four occupations showed a statistically significant association with lung cancer, nasal cancer, or lung and nasal cancer combined, after adjusting for age and calendar time of first exposure and testing for an association with duration in job. The four job categories, as defined by work area or operation, were: the calcining furnace area, the calcining crushing operation, the copper sulfate area, and the Orford furnace area. A nested case-control design was used in which individuals were identified with lung or nasal cancer from the nickel worker cohort, and the controls comprised all of the other workers. In the reduction and volatilization area of the plant, where the ambient nickel carbonyl level was stated to be highest, no significant association was evident for either lung or nasal cancer, nor was there evidence of an association in ten other job categories. Peto et al., however, found an excess risk of lung or nasal cancer for the job categories in the furnaces and copper sulfate areas of the plant. "Low" and "high" exposure were therefore defined on the basis of duration of employment in these two areas of the plant. A worker was considered to have had "low exposure" if he had never worked in the furnaces, and had spent less than five years working in the copper sulfate areas. A worker had "high exposure" if he had spent any time in the furnace area, or had worked for five or more years in the copper sulfate area. The low-exposure group was further divided into two ordinal categories, and the high-exposure group was divided into four ordinal categories.

The SMRs for lung cancer ranged from 340 to 510 for those in the low-exposure groups and from 1,390 to 18,800 for those in the high-exposure groups. These SMRs were found to increase with increasing duration of time spent in the furnaces. In the case of nasal cancer, the SMR was 14,700 to 22,000 for those with low exposures and was 58,800 to 177,200 for those with high exposures. The highest risk occurred for those workers who had spent more than five years in both the furnaces and the copper sulfate areas. For the workers in the high-exposure group, the lowest risks occurred among those who had spent less than two years in the furnaces and five or more years in the copper sulfate areas. Although the higher exposure groups, as defined, showed an excessively high risk of lung and nasal cancer, the risks for these two tumors were not confined to the furnaces and the copper sulfate areas.

Using the same definitions for low and high exposures, Peto et al. showed statistically significant excess risks of death from circulatory disease ($p < 0.05$ for all of the workers between 1902 and 1944), bladder cancer ($p <0.05$ for the high-exposure group), cerebrovascular diseases ($p <0.05$ for the high-exposure group), and respiratory disease ($p <0.05$ for the high-exposure group). The authors noted that the death rate for circulatory disease in South Wales was the highest in Britain, and that if the SMR for cerebrovascular disease is adjusted for local rates, the excess risk completely disappears.

In addition to the job categories of calcining, Orford Furnace, copper sulfate, and crushing, a fifth group labeled "absence" was significantly associated with nasal cancer ($p <0.01$). "Absence" was defined as "the number of years prior to 1925 between first and last employment in the refinery when a man worked elsewhere." The meaning of this variable in terms of exposure is unclear. It could reflect the earlier workers' movement from process to nonprocess jobs, or it could reflect loss of work days due to illness among the older workers. Additional information on these workers would be required in order to interpret the meaning of this variable.

The authors presented a table (adapted herein as Table 8-3) showing "simultaneous" estimates of the dependence of incidence on age at first exposure, period of first exposure, duration in high risk areas up to 1924, and time since first exposure. These analyses were based on internal comparisons using as the "standard category" men with the lowest exposures who had been first employed before age 25 between 1902 and 1910 and who had been observed more than 50 years after first exposure. Nasal cancer showed a strong positive relationship with age at first exposure, whereas lung cancer showed no such relationship. Both lung and nasal cancer showed an increasing risk with increasing duration of work in high-exposure areas. The risk for nasal cancer peaked for the 1910 to 1915 cohort and declined thereafter, whereas the risk for lung cancer was highest for the 1920 to 1924 cohort. The risks of both lung and nasal cancer were low within 20 years of first exposure, and increased up to 40 years after first exposure for lung cancer and 50+ years for nasal cancer.

TABLE 8-3. CLYDACH, WALES NICKEL REFINERS: RELATIVE RISKS FOR LUNG AND NASAL CANCER MORTALITY IN PRE-1925 COHORT, ADJUSTING FOR CONCOMITANT FACTORS[a]

Risk factor		Lung cancer[b]	Significance level p[c]	Nasal cancer[d]	Significance level p[c]
Age first exposed (A)					
<25		1.00	NS	1.00	<0.001
25-34		1.27		2.96	
35+		1.26		10.03	
Period first exposed (P)					
<1910		1.00	NS	1.00	<0.05
1910-1914		1.33		1.81	
1915-1919		0.89		1.31	
1920-1924		1.70		0.60	
Time since first exposure (T) (years)					
<20		0.21	<0.001	0.06	<0.01
20-29		0.61		0.28	
30-39		1.15		0.37	
40-49		1.25		0.75	
50+		1.00		1.00	
Job category (J):					
Time in copper sulfate (years)	Time in furnaces (years)				
0	0	1.00	<0.001	1.00	<0.01
<5	0	1.59		1.27	
5+	0	3.23		2.68	
-	<5	3.16		2.67	
-	5+	4.18		7.18	

[a] Estimated by fitting the equation: Annual death rate = Constant x A x P x T x J.

[b] Value of constant: 0.0048.

[c] For improvement in fit, based on change in log likelihood when each factor is removed from the full (Poisson) model.

[d] Value of constant: 0.0026.

Source: Adapted from Peto et al. (1984).

The results displayed in Table 8-3 can, in part, be an artifact of the cohort definition. Table 8-4 shows that each cohort at Clydach defined by year of first employment differs in both the minimum number of years employed and the minimum number of years between first employment and the beginning of follow-up. As a result, the year of first employment may be highly correlated with duration of exposure and the interval to follow-up, and possibly age at first employment. Given these constraints, any one variable shown in Table 8-3 may not be adequately adjusted for the other three variables. In addition, only individuals first hired during or after 1915 contribute to the adjusted estimate for risks less than 20 years since first exposure. Given the cohort definition, there are no individuals who were first hired before 1915 and who were followed or diagnosed within 20 years of first exposure. Similar problems may exist in estimating adjusted relative risks for other variables shown in Table 8-3.

Finally, Table 8-4 indicates that for the cohort starting before 1910, all lung and nasal cancer cases dying within 25 years since first exposure were not ascertained. As such, the cases ascertained for this cohort are, by definition, late onset cases. This affects the risk estimates for all variables shown in Table 8-3 unless one assumes a constant relative risk by age and/or time since first exposure. In contrast, cases from the 1920 to 1924 cohort who died within 10 to 14 years after first exposure were not ascertained. As such, the cases ascertained in the cohort cover the spectrum from early to late onset cases. If the latency periods for lung and nasal cancer are different and if the relative risk is not constant by age or latency, it is possible that the pattern of risk shown in Table 8-3 is an artifact of the cohort definition.

8.1.1.8 Summary of Studies on the Clydach Nickel Refinery. Changes in the nature and extent of lung and nasal cancer risks are important markers of probable changes in exposures. However, given the variety of modifications in production and control measures, the studies of the Clydach workers to date are limited insofar as assessing these risks with regard to specific nickel species. Other disease risks were also identified in these studies, including circulatory disease, cerebrovascular disease, respiratory disease, and bladder cancer. Additional studies are necessary to determine if these risks are real, and if so, with what work areas or exposures they are likely to be associated.

TABLE 8-4. MINIMUM NUMBER OF YEARS OF EMPLOYMENT AND YEARS BETWEEN FIRST EMPLOYMENT AND THE BEGINNING OF FOLLOW-UP FOR COHORTS FROM THE CLYDACH PLANT, DEFINED BY YEAR OF FIRST EMPLOYMENT

Year of first employment	Minimum number of years of employment	Minimum number of years between first employment and follow-up
<1910	20+	25+
1910-1914	15-19	20-24
1915-1919	10-14	15-19
1920-1924	5-9	10-14

The studies of workers at the Clydach Nickel Refinery reveal the following noteworthy patterns of risk in lung and nasal cancer:

(1) The risk of nasal cancer was found to be highest for workers who began their employment between 1910 and 1914. The risk declined for workers starting after 1914, and no cases occurred among workers starting after 1924.

(2) The highest risk of nasal cancer was found for workers who had spent five or more years in the copper sulfate area and/or the furnace area. The calcining furnace and crushing areas were also associated with an excess risk. In contrast, no excess risk was associated with working in the reduction area, where nickel carbonyl levels were highest.

(3) The risk of lung cancer, in contrast to nasal cancer, was found to be high among workers starting before 1920, and peaked among workers starting between 1910 and 1914. Doll et al. (1977) showed that lung cancer risk was still in excess among workers starting between 1925 and 1929 and, in fact, appeared to be increasing with continued follow-up.

(4) The highest risks of lung cancer were found to parallel those of nasal cancer, with regard to work area, and were associated with work in the copper sulfate and Orford furnace areas.

The use of gauze masks, which were introduced around 1922 to 1923, was the predominant explanation suggested to account for a decline in the risk of nasal cancer. Experimental studies with the masks showed that they reduced the total dust exposure and altered the size distribution of particles penetrating the respiratory system. A single gauze pad was found to have a filtering efficiency of 60 to 85 percent, while two in tandem had 85 to 95 percent efficiency.

Particles most effectively screened were those ranging in size from 5 to 15 μm (International Nickel Company, Inc., 1976). (Typically, particles ranging from 5 to 30 μm are intercepted in the nasopharyngeal region.) If the masks had been used on a continuous basis in the areas of highest risk, workers probably would have received effective protection from exposures to the nasopharynx. No cases of nasal cancer occurred among workers starting after 1924, shortly after the introduction of masks. The risk of nasal cancer, however, seems to have been declining before the introduction of the masks (Peto et al., 1984). In part, this decline could be an artifact of the cohort definition. That is, to meet the cohort definition, workers who started earlier, e.g., 1900 to 1904, had to be employed longer and therefore would have had a higher exposure. The cohort definition forces an inverse relationship between calendar year of first employment and length of employment. As a result, the cumulative exposure for workers defined by calendar year of first employment declined independently of any changes in workplace exposure.

8.1.2 International Nickel Company, Inc. (INCO) Work Force (Ontario, Canada)

Several epidemiologic studies have been done on workers at INCO's nickel-producing operations in Ontario, where sulfide nickel ore is mined and refined at several locations by different processes. The refining processes and exposures are described in greatest detail in the review of the paper by Roberts et al. (1982, unpublished). For additional descriptive background information, the reader is referred to INCO's 1976 supplementary submission to the National Institute for Occupational Safety and Health.

Some important information on processes and facilities is summarized below, while salient points as disclosed in the individual studies are cited in the sections pertaining to those studies. Any discrepancies between reports of dates, etc., should be resolved by industrial hygienists familiar with the INCO history.

The nickel sulfide ores are mined in the Sudbury area of Ontario, from the same nickel deposit as that which is mined by Falconbridge, Ltd. (Epidemiologic findings regarding the cancer mortality experience of Falconbridge workers are discussed following this section on studies of INCO workers in Ontario.)

According to INCO (1976), most of the nickel present in the sulfide ores is found in pentlandite ($NiFeS_2$), with smaller amounts of nickeliferous pyrrhotite (Fe_7S_8). Copper is also present, as are precious metals. Primary processing of the ore is carried out at INCO's Copper Cliff Smelter; until 1972, the Coniston Smelter also conducted some primary processing (Roberts et al., 1983, unpublished). The resulting metallic matte contains primarily nickel subsulfide (Ni_3S_2) and copper sulfide (Cu_2S). Before 1948 (Dr. Stuart Warner, INCO, personal communication), this matte was sent to INCO's refineries in Port Colborne, in southern Ontario, and to refineries in Clydach, Wales. At each of these refineries, the matte was reheated in the presence of oxygen to yield both nickel and copper oxides (Roberts et al., 1983, unpublished). Studies of Clydach workers are reviewed in a separate section of this document, while studies of Port Colborne workers are reviewed in this section on INCO's Ontario operations.

At Port Colborne, nickel was oxidized in calciners supplemented with traveling grate sintering machines, using an open hearth with very high temperatures of approximately 1650°C. This sintering of impure nickel sulfide required the use of fine coke (International Nickel Company, Inc., 1976). The calcining/sintering area of Port Colborne as well as the calcining area at Clydach "were considered the dustiest parts of the respective refineries" (Roberts et al., 1983, unpublished).

At Port Colborne, sintering was carried out from the late 1920s until 1958, while calcining was carried out from 1921 to 1973. A new sintering plant was opened in 1948 at Copper Cliff, the Sudbury area, and continued production until 1964 (Roberts et al., 1983, unpublished) or February 1963 (Sutherland, 1971). "Around this time the oxidation process was being taken over by fluid bed roasters," according to Roberts et al. (1983, unpublished).

The matte processing using fluid-bed roasters produces nickel oxide which is sent to Port Colborne and to Clydach, Wales for further processing (Roberts et al., 1982, unpublished). The work at the Port Colborne Nickel Refinery includes leaching, calcining and sintering, electrolytic, anode furnace, and other occupational subgroups (Roberts et al., 1982, unpublished).

INCO operated a third sinter plant facility in Ontario, at the Coniston smelter. At this plant, finely crushed nickel ores were agglomerated and pre-heated prior to entering the blast furnace, using a lower temperature of approximately 600°C. This low-temperature sintering was carried out from 1914 to 1972 (Roberts et al., 1983, unpublished). This process was the same as that used by Falconbridge, Ltd. until 1978 (Shannon et al., 1983, unpublished).

8.1.2.1. Early Studies. Studies of Ontario INCO workers carried out by Sutherland (1959, 1969) had an important impact on the recognition and quantification of cancer risks among nickel-exposed workers. Additional follow-up of the cohorts of Sutherland's studies was reported by Mastromatteo (1967), Sutherland (1971), INCO (1976), and Chovil et al. (1981). These reports have been reviewed extensively by the National Institute for Occupational Safety and Health (1977a) and Wong et al. (1983, unpublished). The designs of these studies, and their most salient findings, are summarized below.

8.1.2.1.1 Sutherland (1959), Mastromatteo (1967), and INCO (1976). Because these three reports discussed the same study cohort, they will be reviewed together in this section. The study cohort comprised 2,355 men on the payroll at Port Colborne, Ontario, as of January 1, 1930. Sutherland described the cohort as: "All employees with five years or more of service who were on payroll on 1 January 1930 or who subsequently acquired this length of service." All of the men in the cohort therefore had survived at least five years of exposure. Mortality from 1930 through 1957 was ascertained through group life insurance records for refinery employees and pensioners, and through municipal registry offices in and near Port Colborne for employees who had left the plant. Thus, under-ascertainment of deaths would be expected to occur among men who had left the immediate geographic area. Sutherland expected such under-ascertainment to be minimal, "since the study was restricted to 'term-long' employees . . . who might reasonably be expected to be fairly permanent residents of the local community." Death certificates were obtained from local municipal registry offices for deaths occurring from 1930 to 1948. For 1949 to 1957, other records were used, except when deficiencies were found in the information, or more importantly, when cancer was mentioned in the municipal or company records. Various revisions of the International Classification of Disease (ICD) were used to code primary causes of death. The calculation of person-years was not uniform for all workers; men beginning employment after 1930 were counted from the time of hiring, while others were counted from 1930.

Ontario male death rates specific for age and five-year calendar time were used to calculate expected numbers of deaths. An exception is that sinus cancer death rates were available only for the period 1950 to 1957; if sinus cancer death risks in Ontario were actually lower from 1930 to 1949, then the use of the 1950 to 1957 rates would overestimate the expected number of sinus cancer deaths from 1930 to 1949, and would underestimate the SMR.

Men were classified into eight exposure groups, according to their occupations since 1930. Five of the exposure groups were restricted to men with a single exposure, i.e., with a "pure" exposure history: furnace (including cupola, calciners, sinter, and anode furnace workers); other dust (including men with a variety of exposures who had worked for five or more years within the plant, other than in the furnace group, the electrolytic department, or the office staff, in positions such as sinter conveyormen, sulfide unloaders, and weighers, as well as painters, electricians, welders, etc.); electrolytic (presumably having exposure to mists of nickel salts and hydrides); other non-exposure (composed of men in a variety of occupations but not working in the plant); and, lastly, a category for office workers. Three "mixed" exposure groups were created to include men whose employment included work in more than one of the exposure groups; the reasons for changing jobs were not considered in the classification scheme but might have included health problems.

Of the total of 245 deaths ascertained from 1930 to 1957, 19 deaths occurred as the result of lung cancer, while only 8.45 were expected ($p < 0.001$). All of the known lung cancer deaths occurred after 1944, probably due to the fact that the cohort was too young to have experienced lung cancer in the 1930s. Sutherland stated that 76 percent of the person-years were accumulated in employment (rather than retirement) years, and that 65 percent of the person-years were at ages younger than 45. The excess of pulmonary cancer deaths seen after 1944 appeared most strongly in the furnace exposure group (SMR = 380) and the mixed exposure group with three or more years in furnace occupations (SMR = 360), while the "Other Dust" group had an SMR of 220. Reconsideration of the exposure group of the 19 lung cancer deaths and 3 additional cases in order to include occupational history prior to 1930 resulted in reclassification of several cases into the "dusty" categories, which does not change the interpretation of the results.

Nasal sinus cancer was also found in excess among the Port Colborne workers, with 7 deaths observed and 0.19 expected ($p < 0.0001$). The risk appeared to be concentrated among men in the furnace occupations. However, a subsequent update of Sutherland's study with follow-up through 1974 (International Nickel Company, Inc., 1976) indicated that the nasal cancer risk was not limited to furnace workers.

It should be noted that while many of the methods used in Sutherland's study have been criticized in the 1980s, this study was carried out in the 1950s and used techniques that were acceptable at the time. Although the potential biases must be kept in mind when evaluating the results of the study, it is clear that Sutherland's work catalyzed much of the subsequent interest in the risks of nickel exposure.

A brief summary of the results of Sutherland's extension of the follow-up period, reported by Mastromatteo (1967), continued to show excess risk. According to Mastromatteo, major process changes as well as the transfer of sintering operations from Port Colborne to Copper Cliff, Ontario were made as a result of Sutherland's findings.

INCO (1976, unpublished) continued follow-up on 2,328 of the 2,355 workers in Sutherland's 1959 report. Nasal cancer deaths through 1974 increased to 24 (SMR = 5,106, $p < 0.01$), and pulmonary cancer deaths through 1974 increased to 76 (SMR = 1,861, $p < 0.01$). Four laryngeal cancer deaths were ascertained (SMR = 187, $p > 0.05$). Detailed occupational histories of all known cases (not only deaths) of nasal cancer (36) and lung cancer (90) were presented in the 1976 report to address the question as to which exposures were associated with the excess cancer risk. INCO concluded that tankhouse exposure was not associated with lung cancer. INCO also observed that since three cases of nasal cancer at Port Colborne occurred to men without a known occupational history of exposure to any furnace occupation or other dusty job, a year's exposure to sintering or calcining at Port Colborne was not necessary to put a worker at increased risk of nasal cancer. These preliminary observations and conclusions were based on a data set which had the same epidemiologic problems as previously noted regarding the Sutherland (1959) report.

8.1.2.1.2 Sutherland (1969). The sintering operation at Port Colborne was transferred to INCO's Copper Cliff plant, apparently with process changes. For example, no cupola exposure was described at Copper Cliff. The transition began in 1948 and was complete by 1958 (Sutherland, 1971). Sintering of nickel sulfide concentrate to nickel oxide at Copper Cliff was discontinued in February 1963. The Ontario Department of Health carried out a cohort mortality study of Copper Cliff sinter workers who appeared on at least two lists of workers in 1952, 1956, and 1961. Thus, the cohort comprised men with five or more years of experience at Copper Cliff from 1948 to February 1963, but excluded long-term workers in 1952 who did not continue to work through 1956, and also excluded short-term workers between the listed years. The cohort was required to have had at least six months in the sinter plant. Deaths through

June 1968 were ascertained through the company's pension records, which may have caused a possible under-ascertainment of deaths. Causes of death were gathered from death certificates and company records.

A total of 483 men were identified who had served at least six months in the sinter plant. By June 30, 1968, 21 were known to have died, 297 were known to be alive, and a strikingly high proportion were lost to follow-up, i.e., 165/483, or 34 percent. Men who were lost to follow-up because they had left the company contributed person-years until their dates of separation from the company.

Of the 21 deaths, 7 were due to pulmonary cancer, although only 0.78 were expected ($p < 0.05$). The only other cancer death was due to nasal sinus cancer; this was not a statistically significant excess in this small sample, but the length of follow-up was short. Nonetheless, the results did suggest an excess of pulmonary cancer deaths among sinter workers at Copper Cliff.

8.1.2.1.3 Sutherland (1971). To address the hypothesis that the lung cancer and chronic respiratory disease risk among nickel workers was related to the levels of airborne sulfur dioxide generated in the work areas, Sutherland studied workers at INCO's Copper Cliff smelter. A sample was selected by INCO (using an unspecified method) of men who had had at least five years of experience in their respective exposure areas by the end of 1950. The exposure areas and the numbers of men in the sample were as follows:

I. Smelter Converters (n = 246), with the highest exposures to sulfur dioxide and furnace fumes. Exposures included nickel sulfide and nickel oxide.

II. Mill and Separation (n = 172), with low exposures to sulfur dioxide and metallic fumes, except for the exposures incurred by being close to the converter building. Until 1948, the separation process was the Orford process, with nickel sulfide exposure in the cupola furnaces. Since approximately 1948, controlled slow cooling has been used instead of the Orford process, but this process also involves exposure to nickel sulfide. The men in the study may have been exposed to both processes.

III. Tankhouse, Mechanical, and Yard and Transport (Copper Refining Division) (n = 199), with virtually no exposure to sulfur dioxide or metallic fumes.

IV. Frood Mine (n = 225), with no exposure to sulfur dioxide.

V. Eleven of 842 men in the study could not be classified by exposure to sulfur dioxide.

The methods used in this study were similar to those used for the earlier Sutherland reports. Morbidity experience was also followed.

By 1967, 157 men were reported to have died of various causes. Eleven of these deaths were due to pulmonary cancer (SMR = 122). The nonsignificant excess of pulmonary cancer deaths did not appear to be concentrated in any one exposure group, although there were three such deaths among tankhouse workers, compared to 0.94 expected. No mention of nasal cancer deaths could be found in this report.

Although this study gave no evidence of increased risks, several methodological problems may have decreased its ability to demonstrate an increase. These problems include the lack of a clearly defined cohort, the lack of an extensive vital status follow-up (deaths were ascertained through the group life insurance plan), and the influence on the calculation of person-years at risk of past employees whose deaths were not discovered.

8.1.2.1.4 Chovil et al. (1981). Chovil et al. (1981) followed 522 Copper Cliff sinter plant workers with five years of company experience (not all specifically stated to have been in Copper Cliff), including workers who had not been identified in the original cohort of 483 men in the study by Sutherland (1969). This group was stated by the authors to be "not a complete roll of all the sinter plant workers, but a somewhat stratified random selection that included all durations of exposure." Excluded were 10 men who had died before 1963, one of whom had died of lung cancer, and 17 men who were known to have emigrated out of Canada. Thus, the cohort was composed of 495 men who had survived to 1963, were known not to be lost to follow-up, and had been exposed at Copper Cliff sometime between 1948 and 1962.

The cohort was followed for mortality through 1977 in Canada and 1978 in Ontario. Incident cases of lung cancer were identified through the records of the Workmen's Compensation Board of Ontario (WCBO); this may have led to underascertainment of cases who were not in the files of the Compensation Board. The authors identified a total of 54 cases and 37 deaths of lung cancer with expected cases and deaths being 6.38 and 4.25, respectively. To estimate incident lung cancer cases the author multiplied the expected numbers of deaths by 1.5. Eight cases and five deaths of sinus cancer (two of the cases subsequently developed primary lung cancer) were identified in the cohort; expected numbers of cases and deaths for this disease were not reported.

Only 75 percent of 495 men were followed successfully through 1977 or 1978. For the purpose of analysis, the authors counted those lost to follow-up as survivors who did not have lung cancer. This means that the lung cancer risks of

8.5 and 8.7 estimated by the Standardized Mortality Ratio (SMR) and Standardized Incidence Ratio (SIR), respectively, would have been underestimated. The authors found a lung cancer dose response by duration of exposure. They did not find an association between duration of exposure or year of first employment and lung cancer latency.

The poor follow-up, the use of WBCO records to identify incident lung cancer cases, the derivation of expected incident cases, and a somewhat ambiguous cohort definition, are limitations of the study. However, the high overall lung cancer risks among the workers in this study and the lung cancer dose response observed are suggestive of a causal association between employment at the Copper Cliff Nickel Sinter Plant and excess lung cancer risk.

8.1.2.2 Recent Studies. A large cohort mortality study was commissioned as a result of the 1975 Collective Bargaining Agreement between INCO's Ontario Division and the United Steelworkers of America and was carried out by McMaster University. Several reports on the results of this study have been reviewed here (Roberts and Julian, 1982; Roberts et al., 1982, unpublished; 1983, unpublished; 1984).

These reports will be discussed together to describe the basic study design, the overall cohort, and the method of follow-up and analysis. The results will be discussed relative to each group of workers or set of analyses.

The cohort was defined as all men who had worked at least six months for INCO in Ontario, and who were known to be alive on or after January 1, 1950. An exception was that men who had worked in the sinter plant were included regardless of the duration of employment. Men employed exclusively in an office environment away from production facilities were excluded. For this cohort, the earliest and most recent dates of employment were not specified. Presumably the earliest dates could have been as early as the founding of INCO in 1902, or earlier in the companies which joined to form INCO. The men who were alive in 1950 after having been exposed to earlier methods of mining would comprise a selective sample of survivors who might have mortality risks very different from those of other workers. In the case of the most recent dates of employment, if they were within six months of the end of the follow-up period in 1976, then the most recently hired men would not have had a sufficiently long latent period for cancer death. This problem is partially addressed in a subgroup analysis by number of years since first exposure.

A cohort of 54,724 men was identified, of whom 50,436 had worked in the Sudbury, Ontario area and 4,288 had worked in the Port Colborne Nickel Refinery in southern Ontario. The men were classified into 14 occupational subgroups. Mortality through December 31, 1976 was ascertained through the Canadian National Mortality Data Base (described in Smith and Newcombe, 1982), and underlying causes of death from the death certificates were coded using the ICDA, Eighth Revision. SMRs were calculated using age- and calendar year-specific mortality rates for Ontario males.

8.1.2.2.1 Roberts and Julian (1982). This report focused on approximately 30,000 men with some mining experience, and an unspecified number of men in "the entire Sudbury group excluding those men with some experience in the sinter plants because of their known increased cancer mortality." The miners had been exposed to nickel/iron sulfide, copper/iron sulfide, iron sulfide, and small amounts of precious metals. The authors stated that the Sudbury ore contained no asbestos-type material, and that levels of radon daughters had been found to be low in the mines.

Results for the entire Sudbury cohort showed a nonsignificant excess of total mortality (SMR = 104), which decreased when deaths from accidental or violent causes were removed (SMR for all other causes = 96). Among miners with at least 15 years since first exposure, cause-specific SMRs were increased but were not statistically significant ($p > 0.05$) for nasal cancer deaths, SMR = 166 (O/E = 2/1.20) or kidney cancer deaths, SMR = 137 (O/E = 14/10.22); the SMRs were not increased for laryngeal cancer (SMR = 102) or lung cancer (SMR = 105). In the main cohort of Sudbury workers with at least 15 years since first exposure, nonsignificant ($p > 0.05$) excesses of nasal, kidney, and laryngeal cancer deaths were seen (SMRs of 144, 124, and 118, respectively), while a slight excess of lung cancer deaths was observed (SMR = 108, 95 percent confidence interval of 95 to 124). Further analysis by duration of exposure did not suggest that the slightly increased risks occurred only among men with many years of exposure. In fact, the laryngeal cancer excess was seen among workers with less than 5 years of exposure, both in the group of miners (SMR = 125 among those with less than 5 years compared to 93 among those with 5 or more years), and among all Sudbury workers combined (SMR = 248 among those with less than 5 years of exposure compared to 100 among those with 5 or more years).

Two other cancer sites showed interesting results among men with at least 15 years since first exposure. There was some evidence for an increase in pancreatic cancer deaths among miners (SMR = 142, $p < 0.05$). Prostate cancer deaths were also significantly increased among miners (SMR = 167, $p < 0.01$), and showed a gradient of excess with increasing duration of exposure with a very small p value for the SMR among the men with 15 or more years of exposure (SMR = 192, $p = 0.0004$). This finding is consistent with the observations of Enterline and Marsh (1982) and of Shannon et al. (1984) of an increase in cancer of the prostate.

8.1.2.2.2 Roberts et. al. (1982, unpublished). This is a study of Sudbury workers and Port Colborne workers, in which each group was analyzed separately. Sinter plant workers were considered as a separate subgroup in each geographical location. In the Sudbury area, sinter workers were employed at either the Coniston smelter or the Copper Cliff plant.

The report provides informative diagrams of the INCO operations and descriptions of the occupational subgroups. In subsequent papers (Roberts et al., 1983, unpublished; 1984), additional information on processes and dates was presented.

At the Coniston plant in the Sudbury area, sintering was part of the smelting process. Sintering machines were used to prepare the finely crushed ore for blast furnaces by preheating it to the relatively low temperature of 600°C. This smelting process produced a metallic matte containing nickel subsulfide (Ni_3S_2). The process was used at Coniston from 1914 until mid-1972 (Roberts et al., 1982, unpublished), and at Falconbridge Nickel Mines Ltd. of Ontario until 1978 (Roberts et al., 1982, unpublished; Shannon et al., 1984). The sintering at Copper Cliff was part of matte processing. It had been in operation from 1948 to 1964 when the oxidation process was taken over by fluid-bed roasters (Roberts et al., 1984).

At Port Colborne, located in southern Ontario near Lake Erie, nickel copper matte is processed. From 1921 to 1973, nickel subsulfide was oxidized in enclosed calciners. From the late 1920s to 1958, sintering was used with calcining to oxidize the ignited sulfur charge, using traveling grate sinter machines on an open hearth at 1,650°C. The calcining/sintering process was dusty, and is said to have caused exposures similar to those in the calcining sheds at Clydach, Wales. It should be noted that Port Colborne workers who were classified as sintering plant workers included men exposed to leaching and calcining, both of which were carried out in the same location as the sintering.

In the separate analysis of Sudbury workers in sinter plants, 248 deaths were observed, with a nonsignificant overall SMR of 110. A large excess of neoplasia deaths was seen; 74 deaths observed as compared to 41.78 expected (SMR = 177, $p < 0.001$). Among other Sudbury workers excluding sinter plant workers, the overall SMR was 104 (O/E = 4,376/4,218.70). A total of 795 deaths were attributed to neoplasia (SMR = 99).

At Port Colborne, workers in leaching, calcining, and sintering experienced an excess of deaths from neoplasia (O/E = 121/65.52, SMR = 185, $p < 0.001$). For all causes of death, the SMR was 109 (O/E = 366/335.29). These analyses did not take into account any process change in the late 1940s and 1950s, when the sintering process may have been radically altered and began to be transferred to Copper Cliff (Sutherland, 1969). Any excess of mortality attributable to the early, dusty exposures could have been diluted by including men exposed after 1958 only. Other Port Colborne workers did not show an excess of mortality due to any cause, except for a nonsignificant finding for nervous system deaths (O/E = 5/3.51, SMR = 142).

Four sites of cancer were explored in more detail in further analysis as *a priori* or previously implicated sites: nasal sinus, larynx, lung, and kidney. Among non-sinter workers at Sudbury or Port Colborne, no significant excess of deaths due to cancer of the *a priori* sites was seen. Table 8-5 shows the results for the *a priori* sites among sintering plant workers. Statistically significant excesses of lung cancer and nasal cancer deaths were seen at Copper Cliff and at Port Colborne, where the SMRs for nasal cancer were exceedingly high (1,583 at Copper Cliff and 8,000 at Port Colborne), and were also elevated for lung cancer (see Table 8-5). The smaller Coniston plant (where low-temperature sintering was carried out) showed a significant excess of lung cancer deaths (SMR = 286, $p < 0.05$).

One death due to laryngeal cancer was ascertained in a Port Colborne sinter worker, for a nonsignificant SMR of 112 (O/E = 1/0.89). Port Colborne sinter workers also experienced the only kidney cancer deaths (O/E = 3/1.59, SMR = 189, not statistically significant).

Further analysis of sinter workers showed that all the nasal cancer deaths occurred more than 15 years after first exposure. Among Port Colborne sinter workers with at least 15 years since first exposure, the nasal cancer SMR was 16,883 ($p < 0.001$) for those with at least five years of exposure, but was lower for those with less than five years of exposure (SMR = 3,297, $p < 0.001$). The

TABLE 8-5. *A PRIORI* CAUSES OF CANCER DEATHS AMONG ONTARIO SINTER PLANT WORKERS

Sinter Plant	Cancer site											
	Lung			Nasal			Larynx			Kidney		
	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
Copper Cliff	41	9.68	424[b]	2	0.13	1583[b]	0	0.50	--	0	0.92	--
Coniston	5	1.75	286[a]	0	0.01	--	0	0.09	--	0	0.16	--
Port Colborne	50	17.90	279[b]	16	0.20	8000[b]	1	0.89	112	3	1.59	189

[a] $p < 0.05$.
[b] $p < 0.001$.

Source: Adapted from Roberts et al. (1982, unpublished).

dose-response relationship of duration of exposure to nasal cancer death risk at Port Colborne, as well as the very large SMRs, provide strong evidence that the statistical association may be causal in nature. The finding that the excess risk was restricted to workers who had been followed for at least 15 years since first exposure may be related to the latent period required by nasal cancer, as well as to the exposure received by workers whose first exposure occurred in the earlier sintering exposure between the late 1920s and 1958, according to Roberts et al. (1983, unpublished). It should be recalled that the sintering process at Port Colborne was changed and may have been discontinued by 1958, although calcining continued through 1973.

Most of the cases of lung cancer occurred at least 15 years after first exposure (92 of the 97 lung cancer deaths), with a suggestion of a greater excess risk at the Sudbury sintering plants. The excess risk was somewhat higher among those with five or more years of exposure.

Risks among non-sinter workers were not elevated significantly. However, one interesting case raises an important issue in all of the analyses of the Ontario workers. The one nasal cancer death among non-sinter workers at Port Colborne was that of a man who had worked for 20 years in the electrolytic department at Port Colborne. Of particular interest is the fact that he had worked previously for 20 years at INCO's New Jersey plant and had been involved in many roasting/calcining operations; however, he was classified as a non-sinter worker in this analysis. This observation illustrates the problems of misclassification which can arise when complete occupational histories are not taken. Not only can workers with potentially risky exposures be misclassified into low-risk categories, or vice versa, obscuring the differences between job categories, but also the duration of exposure can be underestimated, obscuring dose-response relationships and latency period results. This problem is more likely to occur in locations like the Sudbury area of Ontario, where a man may have worked for two nickel refining companies (e.g., INCO and Falconbridge), while exposure data may only exist for one company. The problem can also occur within a single company, where a worker may have been exposed at two geographically distant locations, yet only one location may be counted. While this misclassification problem may occur in any study of disease risks in the workplace, within-company movement among INCO plants, as well as movement to other nickel-producing companies in the Sudbury area, may have increased the extent of the problem in these studies. Generally, such misclassification problems tend to obscure risks and underestimate SMRs related to specific exposures.

Analysis of additional cancer sites showed an excess of deaths due to cancers of the buccal cavity or pharynx, and of bone, especially among Port Colborne sinter workers (SMR for buccal cavity/pharnynx = 299, $p < 0.05$; SMR for bone = 402, $p < 0.01$). The authors suggest that this result may be due to misclassification of nasal cancer on death certificates. Such misclassification would lead to an underestimate of the SMR for nasal sinus cancer.

An excess of kidney cancer in the Sudbury plants was also suggested, although it was not seen among workers with 20 or more years of exposure. The authors interpret this result as an indication that the risk for kidney cancer "if real, is small and non-specific."

8.1.2.2.3 Roberts et al. (1983, unpublished; 1984). These papers, presented at the 1983 IARC Nickel Symposium, summarize the 1982 report by Roberts et al. and also provide some new analyses. Of particular interest is the reclassification of several cancers to the nasal cancer category, based on additional information. Three bone cancer and two nasopharyngeal cancer deaths were determined to have been misclassified on the death certificates, and actually were due to nasal cancer. All five deaths occurred among Port Colborne workers. Such reclassification generally is not appropriate in mortality studies that must rely on death certificates, since the same reclassification is not applied to the group from which expected numbers are derived. It would seem to be more legitimate with rare cancers such as these, however, in order to allow the best possible estimate of mortality risk. Furthermore, in a situation where a tumor that is rare occurs in epidemic proportions, the probability is increased that any tumor occurring at the same anatomical site is also one of the "rare" tumors.

Nasal cancer mortality rates per 1,000 person-years are shown in Table 8-6 by duration of exposure at the Sudbury sinter plants and the Port Colborne sintering operation. The nasal cancer risk was appreciable at both locations, but was much higher at Port Colborne; among men with at least 15 years since first exposure and with 5 or more years of exposure, the rate was 0.31 per 1,000 person-years for the Sudbury sinter plants, compared to 3.44 per 1,000 person-years for Port Colborne's sintering operation. A weighted least-squares estimate (linear model) of the slope of risk with duration of exposure is 0.030 for Sudbury (95 percent confidence interval of 0 to 0.07) and 0.23 for Port Colborne (95 percent confidence interval of 0.12 to 0.34).

TABLE 8-6. NASAL CANCER MORTALITY RATE AMONG ONTARIO SINTER PLANT WORKERS WITH AT LEAST 15 YEARS OF EXPOSURE, BY DURATION OF EXPOSURE

	Duration of exposure			
	<5 years		5+ years	
Sinter plant	Number of deaths	Rate per 1000 person-years	Number of deaths	Rate per 1000 person-years
Sudbury	1	0.067	1	0.31
Port Colborne	3	0.26	18	3.44

Source: Adapted from Roberts et al. (1983, unpublished).

One of the main observations of this study was that elevated risks of respiratory cancer mortality were not seen among the nearly 48,000 Sudbury workers not exposed to sintering. The authors' calculations of statistical power show that the study had 90 percent power to detect an SMR as low as 121.

8.1.2.2.4 Copper Cliff Medical Screening (Sudbury, Ontario). The finding of an increased respiratory cancer risk among sinter workers at Copper Cliff (Sutherland, 1969) was followed by the initiation of a medical screening program for evidence of lung cancer among exposed men (McEwan, 1976, 1978; Nelems et al., 1979). Because these three reports discussed observations resulting from the same medical screening program, all three will be discussed together in this section.

The screening program was carried out in 1973 and 1974 and included workers who had been exposed to the sintering process at Copper Cliff prior to the 1963 process change. McEwan (1976) presented cross-sectional tabulations of sputum cytology by smoking category, with clinical work-up results for men with positive findings. The clinical findings were updated in a 1978 abstract. Nelems et al. (1979) reported longitudinal follow-up observations on bronchogenic cancer through the end of 1978.

None of the above reports showed any analysis relating level of nickel exposure to subsequent findings of positive sputum cytology and/or cancer. Instead they focused on the use of sputum cytology, per se, in a group presumed to be at increased risk for cancer.

Of the men who worked in the sintering plant at sometime between its opening in 1948 and the major process change in 1963 (more than 483 men, according to other reports), fewer than 300 participated in the 1973 sputum cytology screening program. Recruitment for screening included the following: workers who were still employed at Copper Cliff; former sinter men, whether on pension or employed elsewhere; and men located by a special committee of the local branch of the United Steelworkers of America. None of the reports addressed the question of the relationship between the men in the Sutherland report and the men in this cytology screening program.

McEwan (1976) reported on 282 present or former workers. Cytology results indicated further clinical investigations on 11 of the 282 men. Of the 11, 6 apparently were diagnosed as having squamous cell carcinoma of the lung, while the other 5 men did not have radiographically detectable lesions, but were under medical surveillance. Work exposure histories were not presented, although the author states that this information was gathered. No analysis of the possible relation of nickel exposure to lung cancer or to positive sputum cytology was presented. In 1978, in an abstract summarizing clinical findings (McEwan, 1978), the sample was reported to include 583 men who had participated in the program for one or more years. The relationship of this large number of men to the smaller numbers presented in the 1976 and 1979 papers was not explained.

Nelems et al. (1979) reported on 268 men who had been tested in the 1973 to 1974 sputum cytology screening program. Of these, 12 showed positive cytology by the end of 1978 (11 men were current smokers, while 1 was a former smoker). Ten of the 12 developed lung cancer (squamous cell type), 1 developed maxillary sinus cancer (squamous cell), and 1 developed microinvasive squamous cell cancer of the larynx. The authors did not provide a description of the cohort, nor did they present any data or analysis on nickel exposure levels, time, or age-specific rates of disease. Thus, this study is not of value in the evaluation of the carcinogenicity of nickel.

8.1.2.3 Summary of Studies on the Ontario INCO Mining and Refining Processes.

In summary, studies of INCO's Ontario work force have explored cancer risks associated with most phases of nickel mining and processing. These phases include mining, pyrometallurgical refining of the ore (at Coniston and Copper Cliff), matte refining (Copper Cliff and Port Colborne), and electrolytic refining (Port Colborne). Two major groups of studies have been carried out: the early studies (reviewed in section 8.1.2.1), based on Sutherland's (1959) cohort; and more recent studies, primarily by McMaster University (reviewed in section 8.1.2.2), which used a new cohort definition.

The results of these studies were inconsistent with results found for Falconbridge, Ltd.'s Ontario workers in mining and low-temperature sintering, as well as with results found for Falconbridge, Ltd.'s Norway workers in electrolytic refining of nickel which is presumably from the same deposit in the area of Sudbury, Ontario. (Refer to summary Table 8-10 for SMRs.) On the other hand, INCO workers in matte refining experienced increased risks of lung and nasal cancers, consistent with findings at Clydach, Wales; Falconbridge, Norway; and Huntington, West Virginia. The comparability of study results would be greatly increased if uniform definitions of cohorts and exposures could be applied to the various data sets.

8.1.3 Falconbridge, Ltd., Work Force (Falconbridge, Ontario)

A mortality study of workers employed by the Falconbridge Nickel Mines Ltd., at Falconbridge in the Sudbury area of Ontario, Canada, was carried out by Shannon and co-workers of McMaster University and Falconbridge Nickel Mines Ltd. Three reports of this study have been reviewed here. The first is the unpublished version which was presented at the International Agency for Research on Cancer conference on nickel in Lyon, France in 1983 (Shannon et al., 1983, unpublished). The second was published in the proceedings of that conference (Shannon et al., 1984a). The third was published in a peer-reviewed journal in 1984 (Shannon et al., 1984b). All are reviewed because each presents some material which is not included in the others. Most importantly, the unpublished version (1983) presents many statistical tables which are not included in the other versions, although the conclusions of those analyses of cancer risk remain essentially unchanged. The 1984a paper includes information on process and work environment which is not available in the 1983 manuscript. However, the environmental data are used for descriptive rather than analytical purposes.

The Falconbridge facility employed workers in nickel mining, milling, and smelting. According to the authors, until 1978 the smelting process included a sintering step which was identical to that at INCO's Coniston plant, i.e., low-temperature sintering. Roberts et al. (1983, unpublished) also stated that low-temperature sintering of nickel ore was used at both the Falconbridge and the Coniston plants.

The cohort was identified (Shannon et al., 1983, unpublished) as 11,594 men who had been employed by the company for at least 6 months and who had worked at Falconbridge between January 1, 1950 and December 31, 1976. More than one-third of the cohort had less than two years of exposure at

Falconbridge. These men were followed for mortality and cause of death from 1950 through 1976, using the Canadian National Mortality Data Base as well as independent tracing. The capabilities of the Canadian National Mortality Data Base have been described by Smith and Newcombe (1982). Follow-up was completed on 10,342 men, or 89.2 percent of the total cohort of 11,594.

SMRs for the cohort were calculated based on age- and calendar time-specific rates for Ontario males. SMRs were also calculated for subgroups that included five exposure categories: mines, mill, smelter, service, and administration. Workers were assigned to each exposure category in which they had worked, adding person-years to that category beginning with the date of first exposure. If the workers had died, they also contributed a death to each category of exposure in which they had worked. This method introduced several problems. Some deaths appeared in more than one category, without regard to latency, thus elevating the SMR in several categories. The number of deaths observed in all of the exposure groups combined totals 996, a marked increase over the reported total of 804. Person-years were contributed to more than one category, increasing the number of expected deaths for each category and thus decreasing the SMR. Analyses of time since first exposure were based on time since exposure began, regardless of whether prior exposure had occurred in another category.

The results of the study did show an increased overall SMR of 108 ($p < 0.05$) for all causes of death in all exposure categories combined, while the SMR for cancer deaths was not significantly increased (SMR = 101). Specific causes of death showed a nonsignificant excess for lung cancer (SMR = 123, $p = 0.08$), and a significant excess for laryngeal cancer (SMR = 261, $p = 0.046$), while no deaths from nasal cancer were observed (0.43 expected). The SMR for kidney cancer was 58 (2 observed versus 3.47 expected).

The analysis in the 1983 (unpublished) paper showing SMRs for exposure categories suggests an excess of lung and laryngeal cancer deaths, primarily among men who had worked in the mines, the mill, and/or the smelter, and kidney cancer deaths among men who had worked in the mill (Table 8-7), but not among those who had worked in service or administration. As seen in Table 8-7, the lung cancer excess appeared in all exposure categories (mines, mill, smelter, and service) except administration. The excess among workers cannot necessarily be attributed to nickel, since these workers were exposed to a number of potentially carcinogenic substances. The laryngeal cancer excess was confined to mine, mill, and smelter workers, reaching statistical significance

TABLE 8-7. MORTALITY (1950 TO 1976) BY EXPOSURE CATEGORY FOR LUNG, LARYNGEAL, AND KIDNEY CANCER, AT FALCONBRIDGE LTD., ONTARIO

		Exposure category[a]				
Cause of Death		Mines	Mills	Smelter	Service	Administration
Lung cancer						
	Obs.	28	5	13	20	0
	Exp.	19.65	3.81	9.92	12.34	1.40
	SMR	142[b]	131	131	162[b]	0
Laryngeal cancer						
	Obs.	4	1	1	0	0
	Exp.	1.00	0.20	0.59	0.63	0.07
	SMR	400[b]	507	196	0	0
Kidney cancer						
	Obs.	1	1	0	0	0
	Exp.	1.82	0.37	0.92	1.13	0.13
	SMR	55	274	0	0	0
Prostate cancer	Obs.	2	2	4	1	0
	Exp.	2.58	0.54	1.83	2.07	0.14
	SMR	78	370	219	48	0

[a] Some workers and deaths appear in more than one category, as explained in the text.

[b] $p < 0.05$.

Source: Adapted from Shannon et al. (1983, unpublished): Lung, laryngeal, and kidney cancer statistics from Table 5; prostate cancer (observed and expected numbers) from Table 13.

among miners (SMR = 400, $p < 0.05$). Additional analyses of length of exposure by time since first exposure are difficult to interpret in view of the overlap of workers among exposure categories, as discussed earlier.

Prostate cancer deaths appear to be increased among men who worked in the mills and in the smelter (Shannon et al., 1983, unpublished), as shown in Table 8-7. All four prostate cancer deaths which occurred among smelter workers occurred in men with at least 20 years since first exposure and who had at least 5 years of the exposure itself; the SMR among workers in this exposure subgroup was 302, $p < 0.05$ (Shannon et al., 1983, unpublished). As pointed out by Shannon et al. in the 1984a publication, this excess among smelter workers was consistent with the observation by Enterline and Marsh (1982) of an increase in prostate cancer among nickel refinery workers in West Virginia. Roberts and Julian (1982) also noted an increase in cancer of the prostate among nickel miners in Canada.

Cancer mortality was also increased among workers at the sinter plant, which was closed after 1978. As pointed out by Shannon et al. (1984a,b), the increase in lung cancer mortality among these workers (SMR = 214), although not statistically significant, was consistent with the similar increase among INCO's Coniston sinter plant workers.

In summary, the study provides some evidence for excess risks for several cancers among miners and mill and smelter workers. These findings should be pursued further, with analyses using more refined methods of exposure classification, within the Falconbridge plant. Attention should also be given to occupational exposures in other nickel processing companies in the geographic area. It is entirely feasible that complete occupational histories of Falconbridge workers might show additional exposures at Copper Cliff, for example, which is located less than 25 miles from Falconbridge. Such exposures might have occurred before or after employment by Falconbridge Ltd., and might explain some of the excess mortality in some exposure groups.

The finding of an excess lung cancer risk among Falconbridge sinter workers (SMR = 214), although not statistically significant, is consistent with the excess risk at INCO's Coniston plant, reported by Roberts et al. (1983, unpublished). This consistency adds weight to the epidemiologic evidence of a lung cancer risk among low-temperature sinter workers.

8.1.4 Falconbridge Refinery Work Force (Kristiansand, Norway)

The Falconbridge nickel refinery in Norway opened in 1910, using the electrolysis process to refine nickel ore shipped from Ontario, Canada. The first epidemiologic investigation of risk was reported in 1973 (Pedersen et al., 1973), and was followed by a series of studies up to the present on both cancer risks and biological monitoring.

The refining process begins with Bessemer matte containing approximately 48 percent nickel, 27 percent copper, 22 percent sulfur, and trace metals (Høgetveit and Barton, 1976). The process is divided into five steps: crushing, roasting, leaching of the calcine, smelting, and electrolysis. Over time and particularly since 1950, it has been noted that the production process at Falconbridge has undergone a number of changes, resulting in greatly reduced worker exposures to dust and fumes. Unfortunately, these changes are not specified in the literature. Nonetheless, efforts have been made to characterize the range and types of nickel exposures by category of work. Workers in roasting and smelting operations are primarily exposed to "dry dust," containing nickel subsulfide and oxide, with an average concentration of about 0.5 mg Ni/m^3. The electrolytic workers are exposed to aerosols of nickel sulfate and chloride, with an average ambient nickel concentration of about 0.2 mg Ni/m^3. Other process workers are exposed to miscellaneous nickel composites at an average level of 0.1 mg Ni/m^3. However, the species are not defined for this latter group. Data in these studies on the level of exposure are based on atomic absorption analysis of relatively recent air samples (Torjussen and Andersen, 1979). The relationship between these recent data and past exposures is not known.

Between 1973 and 1983, eleven investigations were reported on the Falconbridge workers. Three dealt strictly with cancer risks in the cohort (Pedersen et al., 1973; Kreyberg, 1978; Magnus et al., 1982). Two studies reported on the relationship between histopathology of the nasal mucosa, nickel exposure, and nickel content of the mucosal tissue (Torjussen et al., 1979a,b). Another five reports were issued on the use of plasma, urine, and nasal mucosa levels of nickel as biological markers of exposure. Finally, one study reported on the use of a serum factor as a possible screening test for nasal cancer risks (Kotlar et al., 1982). Taken together, this set of studies provides what is perhaps the most comprehensive information available on cancer risks from nickel exposure, the relationship between nickel exposure and tissue deposition and retention, and specific associations for various nickel species.

8.1.4.1 Pedersen et al. (1973). This was a study of workers employed for at least three years at sometime between 1910 and 1961 at the Falconbridge Refinery, and who were alive in 1953. A total of 3,232 individuals entered the plant prior to 1971. One thousand nine hundred sixteen met the cohort criteria. A majority (80 percent), started work in the plant after 1944, which meant that the few cases that were missed between 1910 and 1953 were from the earlier and smaller cohort. Exposure was defined by department or category of work of longest employment, and in some analyses by length of employment. However, if someone had been a process worker for several years but had spent more time in a nonprocess job, he was classified as a process worker. The exposure groups and size of each were as follows: roasting and smelting (462); electrolysis

(609); other processes (299); other and unspecified work (546). The last category included laborers, plumbers, fitters, technicians, and administrative personnel. Cancer cases and deaths were identified from the National Cancer Registry and a national mortality file. It is assumed that deaths prior to 1953 were identified and that no one was lost to follow-up. However, it is likely that a number of subjects who died before 1953 were not identified as such and were considered alive during the follow-up period. A total of 48 lung cancer, 14 nasal cancer, and 5 laryngeal cancer cases were identified in the follow-up period. All cases were reviewed and confirmed using hospital records. Expected cancer deaths were based on the age-specific national mortality rates by 5-year age groups for each calendar year during the period 1953 to 1970. Expected numbers of cancer cases were based on age-specific incidence rates for 1953 to 1954, 1955 to 1959, 1960 to 1964, and so forth.

All four job categories were associated with an excess risk of cancer for all respiratory organs combined. However, the SMR for other and unspecified workers was only 190 (95 percent confidence interval of 69 to 414), and, for the most part, was confined to nasal cancer. Workers in the roasting and smelting department showed the highest risk of nasal cancer, with an SMR of 5,000 (O/E = 5/0.1). Two groups showed an excess risk of laryngeal cancer: roasting and smelting (R/S) workers, with an SMR of 1,000 (O/E = 4/0.4), and other process workers, with an SMR of 500 (O/E = 1/0.2). Workers in the electrolysis department showed an excess risk of nasal cancer (SMR = 3,000, O/E = 6/0.2) and had the highest risk of lung cancer (SMR = 812, O/E = 26/3.6). The SMR for lung cancer among R/S workers was 480 (12/2.5). P-values were not reported. However, of the SMRs noted, only the SMR for laryngeal cancer in other process workers was not statistically significant ($p > 0.05$).

It is not possible to estimate median latency for any of the tumor sites because early onset cases (those diagnosed before 1953) were not ascertained for the earlier cohort and the follow-up period for the later cohorts is too short (at most 26 years). However, a comparison can be made of the distribution of cases by calendar time. For the cohort starting employment between 1945 and 1954, the only cohort for which there is complete case ascertainment throughout the follow-up period, one case of laryngeal cancer occurred in each of the three follow-up periods (1953 to 1958, 1959 to 1964, and 1965 to 1971). In contrast, 17 of 23 lung cancer cases and the only nasal cancer case occurred between 1965 and 1971. Five of 14 nasal cancer and 27 of 48 lung cancer cases occurred between 1965 and 1971.

The prevalence of smoking probably increased with each subsequent cohort defined by start date. As a result, the observed and expected values for lung cancer probably increase with calendar time. This may in part account for the distribution of lung cancer cases by calendar time, i.e., a disproportionate number in the later calendar time periods. A lower SMR could be observed even if the overall risk of lung cancer from nickel exposure had not declined. This must be considered when evaluating the magnitude of risk by calendar time.

When analyses are restricted to the roasting and smelting and electrolysis departments, and to the cohort starting between 1910 and 1940, all of the nasal cancer cases are confined to those with more than 15 years of employment. However, given that there was no follow-up before 1953, cases with less than 15 years' employment could have been missed. The SMR for nasal cancer and lung cancer is associated with length of employment (15+ years) for both the 1910 to 1929 cohort and the 1930 to 1940 cohort.

The pattern of risk by cohort and calendar time is incomplete, since cases in the earlier cohort who were diagnosed before 1953 are not included. This is a problem when attempting to summarize the changes in pattern of risk by cohort and calendar time. It is especially difficult if the latency periods for the different tumor sites are different. The picture is further complicated by the increasing age at first employment and decreasing duration of employment for each cohort, as defined by start date. Given these limitations, it is difficult to evaluate latency and risk by duration of work. Nonetheless, some findings from this study are noteworthy. The highest risk of nasal and laryngeal cancer occurred among R/S workers who were primarily exposed to particulates containing nickel subsulfide and oxide. The highest risk of lung cancer occurred among electrolytic workers who were exposed to aerosols of nickel sulfate and chloride. It is noteworthy that differences in risk by category of work were found for different tumors even though the exposure variable was imprecisely defined, i.e., by area of longest duration. The use of more precise definitions of exposure by both category and duration of work may improve the discrimination of tumor-specific risks by exposure setting.

Four of the five cases of laryngeal cancer were first employed on or after 1940, whereas only one of 14 nasal cancer cases occurred among those starting after 1940. It would be of interest to know if changes in the roasting and smelting department are related to the changing risks in nasal and laryngeal cancer, and whether there has been a change in the size and concentration of particulate matter.

8.1.4.2 Høgetveit and Barton (1976). This is a report on biologic monitoring conducted at the Falconbridge refinery for blood and urine nickel levels in 126 R/S workers, 179 tankhouse electrolysis workers, and 187 university students. Nickel levels were measured using flameless absorption spectrophotometry. The average plasma nickel level was higher in electrolysis workers as compared to R/S workers (7.4 μg/l versus 6.0 μg/l). There was no correlation between start date (which is a proxy for duration of exposure) and plasma level. In active workers, plasma levels probably reflect current or recent exposure.

In a comparison group of university students, the average plasma level was 4.2 μg/l, significantly lower than process workers. Plasma nickel levels correlated with urine nickel levels both within individuals over time and by groups. However, plasma and urine nickel can vary widely in an individual and can drop to normal levels two weeks after cessation of exposure.

The authors stated that "the highly soluble nickel salts in the inspired air produced greater biological levels but were more quickly excreted." This statement is in reference to the nickel chloride and sulfate salts in the electrolysis area but was made without knowledge of ambient levels. Subsequent reports showed that even though the total ambient nickel level was lower in the electrolysis area as compared to the R/S area, the plasma levels of electrolysis workers were higher. The data presented in this report are consistent with the conclusions of Torjussen et al. (1979a) summarized below.

8.1.4.3 Kreyberg (1978). This is a case series study of 44 lung cancer cases identified from the Falconbridge refinery. The report is anecdotal and the analysis is somewhat arbitrary. Thirteen cases were excluded because of inadequate material for histologic typing. The cases were divided into two groups; series I cases, who started work between 1927 and 1939; and series II cases, who started work on or after 1946. The cases were diagnosed between 1948 and 1974.

The primary objective of this study was to determine the role of cigarette smoking in the risk of lung cancer among nickel workers. There was no control group, and the conclusions regarding the role of cigarette smoking as a risk factor in lung cancer independent of nickel were based on indirect evidence and anecdotal information. As a result, very little conclusive information can be derived from this study.

Smoking history was obtained in 41 out of 44 cases, and this information was derived from hospital records or patients' statements as noted by laboratory staff. Some of the information included notes on smoking methods and amounts of tobacco smoked. In other instances the statements were less complete, such as "smoked since the age of 6 years" and "heavy smokers." Smoking history does not appear to have been collected in a systematic fashion either from hospital records, the workers themselves, or the next-of-kin.

Kreyberg concluded that "the evidence presented indicates that tobacco smoking is an important additional factor in lung cancer in nickel workers. As a consequence, neither factor can be ignored when the development time is evaluated." This has been noted in the risks of the Clydach plant workers, where the relative risk or SMR declined with calendar time of first employment. Doll (1970) has suggested that part of the decline in the SMR is due to the secular change or secular increase in the amount smoked. In essence, the risk of lung cancer attributable to nickel declines with time only because the risk of lung cancer attributable to smoking and the prevalence of smokers in the population increase with time. As the attributable risk for nickel declines, so does the relative risk.

In summary, the primary conclusion to be derived from this paper is an obvious one for which no direct evidence is provided: When evaluating the lung cancer risks from nickel exposure, one should take smoking into account. It is difficult to determine whether or not a decline in lung cancer risk was due to more controlled conditions in the workplace and the reduction in exposure, or to a decreasing attributable risk for lung cancer from nickel exposure.

8.1.4.4 Høgetveit et al. (1978). This is a follow-up to the 1976 publication on biological monitoring, with an improved method of measuring urine and plasma nickel levels and the addition of ambient monitoring data. Ambient levels were measured by using personal and static samplers. Blood and urine samples were taken before and after work on the first test day and after work on the second and third test days. Two measures of nickel levels were made for each sample. The plasma and urine levels were reported as an average of the eight measures (four samples times two measures each).

A dramatic decline in plasma nickel was shown for workers from before to after the introduction of protective masks. However, levels are presented on electrolysis workers for the "before" measures and on R/S workers for the "after" measures. The conclusion may not be in error but cannot seriously be inferred from the data, especially when a previous report showed that plasma nickel levels were lower in R/S workers.

The correlation between plasma and urine nickel levels was 0.76 to 0.77 for R/S and electrolysis workers. It was lower for nonprocess workers (0.63). In contrast, there was a poor correlation between ambient levels and blood and urine nickel levels. The ambient measures used were from personal samplers. The correlations between ambient and plasma and urine nickel levels for R/S workers were the lowest; workers showed a slightly negative correlation (-0.11) between ambient and plasma levels. The correlations were slightly higher for electrolysis workers (0.31 for urine and ambient levels, and 0.21 for plasma and ambient levels) and highest for other process workers (0.67 for plasma and ambient levels, and 0.47 for urine and ambient levels).

As a group, the electrolysis workers had the highest average plasma and urine nickel levels (11.9 μg/l and 129.2 μg/l), followed by R/S workers (7.2 μg/l and 65 μg/l), and other process workers (6.4 μg/l and 44.6 μg/l). In contrast, the electrolysis workers were exposed to by far the lowest mean air concentration of nickel (0.23 $\mu g/m^3$), followed by other process department workers (0.42 $\mu g/m^3$) and by R/S workers (0.86 $\mu g/m^3$).

This evidence supports the conclusion of Høgetveit and Barton (1976) who suggested that soluble nickel salts, i.e., nickel sulfate and chloride, result in elevated body fluid levels. One other factor worth noting is the relatively high nickel exposure and elevated plasma and urine levels among "other process workers." It would be of some value to more specifically characterize the exposures for this group. Finally, factors which may account for the poor correlation between ambient and body fluid levels of nickel include ingestion, positioning of the worker, and clothing blocking inspiration.

8.1.4.5 Torjussen et al. (1978). This is a study of the concentration of nickel, copper, cobalt, zinc, and iron levels in the nasal mucosa of 30 nickel-exposed and 6 unexposed individuals to determine if a sulfide silver stain was sensitive to the tissue level of these metals. The stain was not found to be sensitive to any single metal, nor to total metal in the mucosal tissue. The results of the test are not relevant to this review. However, the mucosal level of each metal is worth noting.

Workers at the refinery were selected at random. Two subjects with nasal carcinoma and a history of nickel exposure were also selected. Twenty-five of the 30 workers were from either the electrolysis or the R/S departments. The average ages of R/S and electrolysis workers were 53.5 and 52.9, respectively. Controls were considerably younger (mean = 39.7). Five were involved in other work at the refinery. The six controls presumably had never been employed at the plant. All biopsies were taken from the middle nasal turbinate.

As a group, the exposed subjects did not have a statistically significant higher mean concentration of mucosal nickel than did the controls, even though the means were 354 and 21, respectively. The standard deviation for both groups was extremely high. In contrast, the mean nickel level for the 11 R/S workers was significantly higher than that of other workers. In addition, the mucosal levels of copper and zinc were also higher among R/S workers. However, no statistical test was conducted.

In summary, the results on mucosal nickel levels are consistent with other investigations. It is of interest to note the higher content of other metals among R/S workers. It is not well established how these other metals are related to workplace exposures.

8.1.4.6 Torjussen and Andersen (1979). The primary objective of this study was to obtain quantitative data on active and retired nickel plant workers and unexposed controls regarding nickel levels in the nasal mucosa, plasma, and urine, and the relationship of this information to duration of exposure. Four groups were selected for study: a random sample of workers employed for at least 8 years at the nickel refinery in the crushing, roasting, smelting, or electrolysis areas as of October 1976; a 20 percent random sample of nonprocess workers; 15 male pensioners; and 57 age-matched unexposed subjects selected from a local hospital. Out of a total of 370 current and former refinery workers invited to participate in the study, 318 participated. The average age and time from "first" nickel exposure were similar among roasting and smelting workers, electrolysis workers, and nonprocess workers.

The average plasma nickel levels were much higher among the electrolysis workers (8.1 µg/l ± 6.0) as compared to the R/S workers (5.2 ± 2.7) or the nonprocess workers (4.3 ± 2.2). The same pattern was found for urine nickel levels. In contrast, the R/S workers had a significantly higher average nickel content in the nasal mucosa (467.2 µg/100 g), and, surprisingly, the electrolysis workers had the lowest mucosal nickel levels. The plasma, urine, and mucosal nickel levels of retired workers were between those of the active workers and the unexposed controls. In general, tissue nickel levels were not correlated with either plasma or urine nickel levels among active workers. In contrast, significant correlations were found in the 15 retired workers.

The authors noted the "highly significant correlations between duration of nickel exposure and plasma, urine, and mucosal levels." Correlation coefficients appear to have been derived within each category of work and for total duration of exposure to nickel for all categories combined. Duration of exposure in the R/S workers was significantly correlated with nasal mucosal levels only. In contrast, duration of work in the electrolysis area was highly correlated with plasma and urine levels, but was negatively correlated with nasal mucosal levels. The correlation coefficients for overall duration of nickel exposure were significant ($p < 0.01$); however, all were lower than the coefficients derived by the specific categories of work.

A half-life for retention of nickel in the nasal mucosa was derived from the data on retired workers. Using length of time since retirement and mucosal nickel level, a half-life of 3.5 years was estimated. It should be noted, however, that this estimate was highly dependent on measures from a single subject ten years after retirement, and should therefore be considered unreliable. It would be of interest to know the mucosal nickel levels in this group at sometime in the future to better estimate the tissue half-life.

Exposure status was based on the subject's current job as of November 1976, and not on the job of longest duration. This definition of exposure may be most relevant for plasma and urine nickel levels, which are more likely to reflect current and recent exposure status. In contrast, the nickel level of the nasal mucosa may reflect both past and current exposure, and an exposure definition based on jobs of longest duration may be more relevant. If there is a low rate of movement between departments, the results will be essentially the same when using current versus longest job. A more definitive analysis could have been done by defining the length of time spent in each category of work and adjusting the category-specific coefficients for the length of time spent in other work categories.

In summary, this investigation provides information that is consistent with the mortality study summarized previously. The highest tissue nickel levels occurred among the R/S workers who were predominantly exposed to dust containing nickel subsulfide and oxide. As the authors suggested, this pattern is consistent with the expected deposition pattern in the upper respiratory system. In contrast, electrolysis workers who were primarily exposed to aerosols of nickel chloride and sulfate had the highest urine and plasma nickel levels. Whether this was related to a higher deposition of the aerosols in the lungs and more ready absorption of these water-soluble nickel species was not determined. The tissue nickel level of retired workers was between that of active and unexposed workers. One can infer a time-dependent release of nickel from the tissue. The half-life is uncertain, however, and warrants further investigation.

8.1.4.7 Torjussen et al. (1979a). This was a study of histopathology of the nasal mucosa among nickel refinery workers, non-nickel industrial workers, and subjects without industrial exposure. Ninety-eight male nickel workers were selected, of which 91 were active workers and 7 were retired or former workers. Three of the seven were diagnosed during the study as having nasal carcinomas. Exposed workers were divided into three groups: crushing, roasting, and smelting (n = 55), electrolysis department (n = 28), and other process workers (n = 15). Individuals were divided into groups defined by work area of longest employment or highest exposure. Sixty-one subjects without a history of nickel exposure comprised the control group. Sixteen were employed in an electrochemical plant which was described as "dusty." The remainder were hospital patients or military recruits. The average age was 50.1 for the nickel-exposed group and 37.5 for the unexposed group.

Nasal biopsies were from the middle turbinate and from the cavity "with the best air passage or side where the pathologic changes were mainly located." All biopsies were graded blind on an eight-point scale ranging from normal respiratory epithelium to carcinoma. Two readings were made on each biopsy, presumably by different readers. There was exact agreement in 148 of 159 samples (93 percent). Three histologic groups were defined: normal (0), limited to moderate changes (1 to 5), and dysplasia to carcinoma (6 to 8).

Twenty-five subjects had a grade of zero, 22 of which were from the non-industrial group. Twenty-two subjects had a grade of 6 to 8, all of whom were nickel workers with 10 or more years of employment. Individuals with 10 to 19 years in the nickel refinery had the same average grade and distribution by grade as workers employed 20 years or more. Workers in the R/S and electrolysis departments had similar average histologic scores, both of which were higher than other process workers. Six of 15 R/S workers had scores in the most severe category (6 to 8), all of whom had severe dysplasia or carcinoma (scores of 7 to 8). In contrast, the seven electrolysis workers with the most severe grade had scores of six. No relationship was observed between histologic score and smoking status.

The results are consistent with the higher risk of nasal cancer among the R/S workers observed in other studies. However, no information on age at first employment and length of employment by category of work was given, although both variables are related to histologic score. Simple and partial correlations between histologic score and a number of variables were described. Data from all 159 subjects were used, and given the wide differences in the age distribution of exposed workers and controls, it may not be possible to adequately adjust for age in the analysis. Nonetheless, partial correlations for R/S and electrolytic process work with age and years from first exposure were statistically significant.

8.1.4.8 Torjussen et al. (1979b). This was a study of the relationships between histopathology of the nasal mucosa and exposure to nickel, age, smoking status, and nickel level in the nasal mucosa, plasma, and urine. The objective and methods were essentially the same as in the pilot study described above (Torjussen et al., 1979a). The population and methods are described by Torjussen and Andersen (1979). Plasma and urine nickel levels were included in addition to the variables described in the pilot study.

A smaller percentage of active compared to retired workers had histologic scores greater than five, i.e., epithelial dysplasia or carcinoma. Twelve percent of the R/S workers, 11 percent of the electrolysis workers, and 10 percent of the nonprocess workers exhibited epithelial dysplasia, i.e., a score of 6. All but one of the nonprocess workers with dysplasia were former process workers. Two percent of the R/S workers (n = 25) had carcinoma *in situ*, i.e., a score of seven. No other active workers had a score greater than six. Fifty-three percent of the retired workers had a score of between 0 and 5, and the remaining 47 percent had a score of 6. Among the controls, only one subject (2 percent) had a score of greater than five. The average histologic score was highest for retired workers (4.93), followed by R/S workers (3.25), electrolysis workers (3.01), and nonprocess workers (2.49). The average score among the controls was 1.88.

The average histologic score increased with age among active nickel-exposed workers, but not among the unexposed controls. Since age is probably correlated with length of exposure, this pattern would suggest that changes in the nasal mucosa are primarily correlated with duration of exposure.

Simple and partial correlation coefficients were estimated between a number of dependent variables and the histologic scores. Statistically significant partial correlation coefficients were found between histologic score and R/S work, electrolysis work, and age. In contrast to the pilot study, the partial correlation in this study was not significant according to years from first nickel exposure, but was significant for amount smoked.

Several factors probably account for the differences between the pilot study and the more extensive investigation described above. The exposed and control groups differed in definition and size. The larger investigation was limited to workers with at least eight years of employment in the plant. As a result, there was probably less variation in length of employment and a greater average length of employment. This may be responsible for the absence of a significant partial correlation between histologic score and time since first employment. The control group was not matched for age in the pilot study (Torjussen et al., 1979a), as it was in the larger investigation.

8.1.4.9 Høgetveit et al. (1980). The purpose of this study was to investigate the diurnal variation in urine and plasma nickel levels and its relationship to ambient levels. Three workers were selected from both the R/S and electrolysis departments. No protective masks were worn during the test period. Blood, urine, and personal air monitoring samples were taken every hour from the start to the end of the working day.

Hourly urine nickel levels were found to be highly variable within an individual. As a result, single measures are thought to be unreliable as a marker of recent exposure. One factor which may contribute to the high variation, as the authors noted, is the greater risk of contamination of urine samples in contrast to blood samples. Plasma nickel levels in electrolysis workers tended to increase throughout the day and were, on the average, higher than those of the R/S workers. In contrast, the ambient nickel levels in the R/S department were more than twice the level in the electrolysis department.

In summary, the results of this study are consistent with other investigations of the relationship between body burden, work setting, species of nickel exposure, and ambient levels. In addition, a single urine sample is probably inadequate to measure the body burden from recent nickel exposure. A single plasma sample will probably yield a more reliable relative estimate of recent exposure to nickel.

8.1.4.10 Magnus et al. (1982). This was an update of the study reported by Pedersen et al. (1973). The follow-up period was extended to 1979 for a total of 26 years of follow-up, an increase of 8 years. The study group included all men starting employment before 1966 who were alive on January 1, 1953, and who had been employed for at least three years. The problems with such a cohort definition have been noted in the above review of the Pedersen et al. (1973) paper. A total of 2,247 subjects met the cohort criteria, and during follow-up, 82 lung cancer, 21 nasal cancer, and 5 laryngeal cancer cases were identified. In addition, smoking histories were acquired for almost all of the cohort members. However, information on smoking status only and not on amount smoked was used, and individuals were classified simply as present and past smokers (ever smoked) or nonsmokers. Analyses were presented by job category, calendar time of first employment and years since first exposure, and smoking and nickel exposure status.

SMRs in four job categories were determined for nasal cancer, laryngeal cancer, and lung cancer. The four job categories were roasting and smelting, electrolysis, other specified processes, and administration/service and unspecified. An excess risk of nasal cancer was shown in all four job categories. The highest SMR (4,000, O/E = 8/0.2), was in the roasting and smelting category, followed by 2,600 (O/E = 8/0.3) in the electrolysis category, 2,000 (O/E = 2/0.1) for other specified processes, and 1,500 (O/E = 3/0.2) for administrative jobs. Only two categories showed an excess risk for laryngeal cancer. The R/S workers had an SMR of 670 (O/E = 4/0.6), and other specified process workers had an SMR of 330 (O/E = 1/0.3). Only one case was identified in the latter category. No cases of laryngeal cancer were identified in the electrolysis group or the administrative group. The pattern for lung cancer was somewhat different. The electrolysis group showed the highest SMR, 550, which was followed by an SMR of 390 (O/E = 12/3.1) for other specified process workers, and an SMR of 360 (O/E = 19/5.3) for the R/S group. The administrative group showed an excess risk, but it was relatively low with an SMR of 170 (O/E = 11/6.3). The higher risks of nasal cancer and laryngeal cancer among R/S workers are consistent with the results from studies that have shown this group to have had the highest concentration of nickel in the nasal mucosa. In contrast, the electrolysis group, which was shown to have had the higher plasma and urine levels of nickel and had typically been exposed to aerosols of nickel sulfate and chloride, showed a higher risk of lung cancer.

Observed-to-expected ratios were displayed by year of first employment and number of years since first employment. (These dates may not correspond, however, to year of first exposure and time since first exposure.) No nasal cancer cases occurred within 3 to 14 years of first employment, even among the cohorts which started work later, e.g., 1940 to 1949, 1950 to 1959, and so forth. For a fixed number of years since first employment (i.e., 3 to 14, 15 to 24, 25 to 39, and 35+), there was a consistent decrease in the SMR as the year of first employment increased. This suggests that exposure to the carcinogen which caused nasal cancer could have been decreasing with calendar time either because ambient levels decreased or the duration of exposure was shorter in more recent cohorts.

The pattern of risk for lung cancer is somewhat different from that described for nasal cancer. Excess risks can be found within 3 to 14 years of first employment. Later cohorts, i.e., those starting in 1940 to 1949 or 1950 to 1959, showed a peak SMR 15 to 24 years after first employment, whereas the earlier cohort, i.e., those first employed between 1930 to 1939, showed a peak 25 to 34 years after first employment. The risks within subgroups defined by year since first employment do not consistently decline with calendar time, as was shown for nasal cancer. The pattern of risk for lung cancer is somewhat difficult to explain. The later cohorts, which might be expected to incur a lower exposure, experienced shorter latency periods. The authors suggested that the patterns noted may have been due in part to the changes in smoking habits with calendar time, or, as suggested by Kreyberg (1978), to the increasing age of first employment with calendar time.

The authors assessed the combined effects of smoking and nickel exposure on the risk of lung cancer, and concluded that the effects are likely to be additive since the risk ratio of smokers to nonsmokers is 5.9 for non-nickel workers and 2.0 for nickel workers. If interaction were operating, the risk ratio among nickel workers who smoke would be much higher than that among nickel workers who do not smoke. The inference with regard to an additive effect might be more direct if expected rates among smoking and nonsmoking nickel workers were derived by applying the age-specific rates of the survey population to the age-specific distribution of person-years among each of the smoking and nonsmoking nickel workers. If the differences between the observed and expected rates were equivalent for the smoking and nonsmoking nickel workers, one could infer a simple additive model.

The results of this study are consistent with the 1973 report. Interpretation of SMRs by start date is simplified, however, because time since first employment and not calendar year is used. The relationships between job category and tumors of highest risk are consistent with the previous report.

8.1.4.11 Kotlar et al. (1982). This was an investigation of the utility of a medical screening test, a serum antigen, for nasal and lung cancer. The study provided no information on the risk of lung or nasal cancer, either by species of nickel exposure or from nickel exposure in general. Four groups were selected for study. These were: 18 randomly selected current employees who had worked at the Falconbridge refinery for 6 to 10 years; 33 randomly selected active workers who had been employed for more than 10 years; 17 randomly selected office workers with no refinery work experience; and 6 cases with nasal carcinoma of the squamous cell type, 2 of whom had an occupational history of nickel exposure. Nasal biopsies were obtained from all subjects, and histological grades were assigned. Questionnaire interviews were administered to obtain occupational histories, including duration of work in the nickel industry and information on habits and medical histories.

The mean ages of each group were 51 for the controls, 38 for the short-term workers, 54 for the long-term workers, and 70 for the nasal cancer cases. The subjects were tested for three antigens: lung cancer, nasal cancer, and breast cancer. The breast cancer antigen was included as a non-specific marker. The percentages of positive responses to the lung, nasal, and breast cancer antigens were higher for the nickel-exposed workers than for the non-exposed workers. The long-term workers showed more positive responses than the short-term workers. The six subjects with nasal cancer had the highest percentage of positive responses for the lung and nasal cancer antigens. These differences may have been due in part to differences in age, since the percentage of positive responses correlated with age.

The authors concluded that the "present data strengthens the usefulness of the H-LAI test for identification of individuals with a high risk of cancer." The results of the study, however, do not support such a conclusion. The sensitivity of the nasal cancer antigen was good (83 percent) for the cases with nasal cancer. However, the specificity of this test was essentially unverified, and given the number of positive responses to all three antigens, it is likely that the specificity was extremely poor unless the risk of nasal cancer among current workers is on the order of 20 to 30 percent, much higher than would be expected under present conditions. In addition, age was not effectively controlled in this study.

8.1.4.12 Summary of Studies on the Falconbridge Refinery (Norway). The studies on cancer risk, in combination with the numerous studies on biological monitoring, provide valuable information on the association between the risk of nasal and lung cancer and specific nickel species.

The highest risk of nasal cancer was found to occur in R/S workers who had been exposed primarily to particulate matter containing nickel subsulfide and oxide. This association is corroborated by the fact that R/S workers currently have the highest nasal mucosal nickel levels and the highest frequency and severity of nasal mucosal dysplasia. The highest risk of lung cancer occurred in electrolytic workers who had been exposed primarily to aerosols of nickel sulfate and chloride. The nasal mucosal levels of nickel were the lowest in the electrolytic tankhouse workers. In contrast, the urine and plasma levels, which for the most part reflected current or recent exposure, were highest. The exposures of other process workers were not well defined, and it would be of some use to better characterize their exposure and associated risks.

The occurrence of laryngeal cancer and the disappearance of nasal cancer appear to have been associated. Four of the 5 laryngeal cancer cases were first employed during or after 1940, whereas only 1 of the 14 nasal cancer cases occurred among those starting after 1940. The refinery appears to have been inactive between 1940 and 1945. It would be of interest to know what changes in production and control measures were introduced, and the relationship of such measures to changes in dust particle exposure and distribution and nickel species exposure. As an alternative explanation, the increased risk of laryngeal cancer could reflect changes in smoking patterns. However, data were not presented to address this question.

Two methodological problems present some difficulty in the interpretation of risks on the basis of these studies. Exposure groups were defined on the basis of work area of longest duration or highest exposure, whereas duration of exposure was, for the most part, defined as total length of employment. Using these exposure criteria can result in heterogeneously defined exposure groups, and it is possible that the risks associated with certain work areas may have been due, in part, to exposures incurred while being employed in other work areas. Defining exposure more precisely can only improve the understanding of tumor-specific risks associated with different exposure settings. A second problem is related to the definition of the cohort and the loss of early-onset cases. Approximately one-third of the total cohort was first employed between 1916 to 1949. Follow-up did not begin until 1953. As a result, earlier-onset cases from the pre-1950 group were missed. It is likely that these methodological problems affect the magnitude of risk estimates but not the relative order of risk by exposure category.

8.1.5 Hanna Miners and Smelting Workers, Oregon (U.S.A.)

Cooper and Wong (1981, unpublished) reported on a nonconcurrent prospective study of an incidence cohort of 1,307 men employed for at least 12 months at the Hanna Nickel Smelting Company between June 1954 and December 1977. The ore mined and processed in Oregon is sulfur-free. According to the authors, workers are not exposed to arsenic, nickel sulfide, or nickel carbonyl. In this report, documentation of exposure and description of the cohort are excellent, and the analysis is complete and straightforward.

The follow-up period was from 1954 to 1977, for a total of 24 years. Of the cohort, 21 (1.6 percent) were lost to follow-up. One hundred twenty-nine deaths were identified in the follow-up period, of which 12 were due to lung cancer and 2 to laryngeal cancer. No nasal cancer cases were identified.

Personnel records were used to identify the jobs held by each worker. Each job title was classified into one of four exposure categories, and individuals were categorized by exposure groups as defined by the job title and length of time the job was held. The industrial hygiene data used had been collected by the U.S. Public Health Service in 1967 and by the National Institute for Occupational Safety and Health in 1976. According to Cooper and Wong, the ambient nickel levels measured were relatively low for both periods. Twenty-two samples were collected in 1967 in the smelting building. All were below the threshold limit value (TLV) of 1.0 mg/m^3 as a time-weighted average. Four were above 0.1 mg/m^3; 15 were below the 0.01 detectable limit. The survey in 1976 was based on 81 samples in which the nickel ranged from 0.004 to 0.420 mg/m^3. Six percent of the samples were above 0.1 mg/m^3, and 22 percent were above 0.01 mg/m^3. A number of controls were introduced between 1954 and 1967, before the first ambient measures were made. These controls included dust filters installed on the melting furnaces, crusher house, and storage bins in 1958, and electrostatic precipitators, which were installed on the calciners, the wet scrubbers, the dryers, and the ferrosilicon furnace. A total of 342 workers were employed at the highest exposure level for at least 12 months. Five hundred fifty-seven were never exposed in the highest exposure group. Expected values were derived using rates for U.S. white males. Analyses were presented by calendar time of first exposure, level of exposure, and location of work.

The overall SMR was 78, significantly less than 100 ($p < 0.05$). No nasal cancer cases were identified, but only 0.07 were expected. The SMR for lung cancer was slightly in excess of that expected (SMR = 105), but was not statistically significant. The SMR for laryngeal cancer was 380 among all workers and was 393 among those who had ever worked in the smelter, refining furnaces, skull plant, or ferrosilicon area. Neither of these SMRs was statistically significant. A statistically significant SMR was found for laryngeal cancer among employees observed 15 or more years after their hire date (SMR = 909, $p < 0.05$). Analysis by latent period did not result in any differences from the overall SMRs for lung or laryngeal cancer; however, the group with the longest follow-up period had a maximum follow-up of 24 years and included both exposed and unexposed workers. In addition, there were only 1,192 person-years of follow-up more than 20 years after exposure. The SMR for lung cancer, more than 20 years after first exposure, was 215, which was not statistically significant. No statistically significant excess risks were found for lung cancer or other causes for the highest exposure group. In fact, the highest SMR was found in the lowest exposure group. In addition, no excess risk was shown by location of work, whether in the mines or the smelting areas.

The results suggest that there was no excess risk for lung, nasal, or laryngeal cancer from nickel exposure at the Hanna facility. However, given the relatively small statistical power of the study, and the short follow-up period used, the conclusions are somewhat limited. The authors indicated that the study had an 80 percent power of detecting an SMR for nasal cancer of 8,900. Another consideration with regard to this study is related to the ambient levels of nickel and the length of employment in the highest exposure groups. The combination of low ambient nickel levels and short-term employment in high-exposure groups resulted in relatively low exposures, even among those defined as the high-exposure group.

8.1.6 Nickel Refinery and Alloy Manufacturing Workers, West Virginia (U.S.A)

This was a study of the disease risks in a cohort of workers at a nickel refinery and alloy manufacturing plant in Huntington, West Virginia, by Enterline and Marsh (1982). This plant received matte from an INCO smelter in the area of Sudbury, Ontario. Three groups of workers were defined for study: those hired before 1947, who had worked a year or more in the refinery, and who were working there at sometime during 1948 (n = 266); workers with the same characteristics as defined above, but who had worked in the refinery area for less than a year (n = 1,589); and those hired after 1946 (less than one year before the calciners were shut down). The first two groups had the highest nickel exposures.

The refinery consisted of two departments: 1) calcining, and 2) melting and casting. The calcining department operated from 1922 to 1947. Matte for the refinery was obtained from a Sudbury smelter, and was a "high copper-nickel matte." The concentration of total particulates was found to be "very high" where the matte was crushed, ground, and handled, and lower around the calciners (20 to 350 mg Ni/m^3 and 5 to 15 mg Ni/m^3, respectively). Vital status of cohort members and cases was determined through company records, and follow-up was carried out through the Social Security Administration, the Veterans Administration, the U.S. Postal Service, and direct telephone inquiries. The period of follow-up was from January 1, 1948 to December 31, 1977, a total of 29 years. Sixty-five lung cancer, 2 nasal cancer, and 2 laryngeal cancer deaths were identified. Expected values were derived using five-year age- and calendar time-specific mortality rates by cause for white males nationally and locally. Exposure groups were defined in several ways: by the cohort definitions noted above, by duration of employment, and by cumulative nickel exposure.

The refinery workers had elevated SMRs for nearly all causes (in contrast to nonrefinery workers), ranging from a low of 86.2 for heart disease to a high of 181.8 for "other malignant neoplasms." The SMR for nasal cancer was the only one to exceed 200 (SMR = 2,443.5), with 2 observed and 0.08 expected cases. However, there was no large excess of lung cancer among refinery workers (SMR = 118.5); the SMR was slightly lower among non-refinery workers (107.6), and was highest among those hired after 1946. Nasal cancers were exclusive to the refinery workers. Restricting the analysis to workers followed 20 or more years after first exposure did not change the SMRs appreciably. There was no apparent relationship between duration of work and SMR for lung cancer; however, the analysis included both refinery and non-refinery workers. The highest SMR found was for workers employed 20 to 29 years (SMR = 119.3), and the lowest was for those who had worked for less than 20 years (SMR = 64.1).

All of the nickel workers were assigned cumulative nickel exposure estimates based on department and duration of work shown on the subjects' personnel records. When all respiratory cancer cases were combined and cumulative nickel exposure was restricted to the 20 years after first exposure, there was a dose-response relationship across four exposure categories, with an SMR of 161.1 in the highest cumulative dose group.

This study showed an excess risk of nasal sinus cancer among nickel refinery workers. Surprisingly, there was no significant excess of lung cancer. However, a measurable dose-response relationship was shown between cumulative nickel exposure and lung cancer, although the SMRs were generally low in contrast to those of other studies. Enterline and Marsh suggested that the actual exposure level at the Huntington plant may have been considerably lower than that reported at plants where larger excess risks had been reported.

8.1.7 Sherritt Gordon Mines Workers (Alberta, Canada)

Hydrometallurgical nickel-refining operations were begun at Fort Saskatchewan, Alberta, in 1954. In the refinery, nickel was recovered from concentrates in a process which produced complex metal amines, copper sulfide, nickel sulfate, and pure metallic nickel powder. Further refining of the remainder produced nickel sulfide and cobalt sulfide. In another operation at the same plant, nickel powder was treated and compacted into briquettes or fabricated nickel strips. Air sampling began in 1977 (Egedahl and Rice, 1983, unpublished; 1984), and showed high to moderate levels of airborne nickel dust in specific locations in the plant.

Egedahl and Rice (1983, unpublished; 1984) carried out a nonconcurrent, prospective study of cancer incidence and mortality among men who had been employed for at least 12 consecutive months at Sherritt Gordon Mines between January 1, 1954 and December 1978. Active employees, retired pensioners, and terminated workers were included in the study. Two groups of workers exposed to nickel were identified: (1) 720 men who were employed in the nickel refinery processes, and (2) 273 maintenance employees, including steamfitters, welders, painters, and others. The vital status of the past employees was ascertained as of the end of 1978 through "traditional information sources" and the Alberta

Health Care Insurance Commission, with confirmation of the vital status on a total of 94 percent of the cohort. Cancer cases were identified by the Alberta Cancer Registry, and deaths among those cases were verified by the Alberta Vital Statistics Division.

Expected numbers of cancer cases were calculated using age- and calendar time-specific incidence rates for males in Alberta, Canada. Rates for 1964 to 1968 were applied to the person-years accumulated from 1954 to 1964 because the actual rates were not available. It should be noted that the expected numbers of cancer cases would be overestimated if cancer death rates actually increased in the later time period as they have done elsewhere; this would inflate the denominator of the SMR and produce an underestimate of the SMR.

The results showed no cases of nasal cavity, paranasal sinus, laryngeal, or lung cancer among the 720 nickel process workers. Two cases of lung cancer occurred among 273 maintenance workers, both of whom were smokers who had been exposed to nickel concentrate, soluble nickel compounds, and metallic nickel in the leaching area. The SMR for lung cancer among maintenance workers was 175, which was not statistically significant ($p < 0.05$, O/E = 2/1.14). Renal cell cancer showed an SMR of 303 (O/E = 1/0.33) among nickel workers, 370 (O/E = 1/0.27) among maintenance workers, and 333 (O/E = 2/0.60) among all workers combined, none of which were statistically significant ($p < 0.05$). Both of the two men with kidney cancer had worked in the leaching area, where they had been exposed to nickel concentrate, soluble nickel compounds, and metallic nickel, and both were smokers.

The authors concluded that no association was seen between nickel exposure and lung or nasal cancer. However, the ability of this study to detect an association is small. The cohort was not large (993 total), and most of the men in the cohort were young. Ninety-one percent of the person-years among the nickel workers were accumulated under age 50, and 79 percent of the person-years among the maintenance workers were accumulated in that younger age group.

8.1.8 Nickel Refinery Workers (U.S.S.R)

Two studies of cancer mortality among nickel refinery workers in the U.S.S.R. were reported by Saknyn and Shabynina (1970, 1973). In the 1970 report, a plant in the Urals which refines oxide ore was studied. The processes used included drying-and-pressing, smelting, roasting-reduction, and briquetting, but not electrolysis. Exposures included sulfide and oxide nickel in the pyrometallurgy production shops, and cobalt and arsenic in the cobalt shop.

The cohort under study apparently comprised persons "in the personnel roster books of the combine, beginning with its foundation." The authors characterized the plant as "one of the oldest nickel combines in the Urals," but did not give the year in which it was opened. Follow-up appears to have been carried out "by family," based on information in the company's archives. Cancer mortality from 1955 to 1967 among workers was compared to that in the urban population of the area as a whole according to age and sex groupings. Cancer mortality among the workers was also compared with that in (1) the local oblast (an oblast is a political subdivision of a Soviet republic); (2) the Russian Soviet Federated Socialist Republic (RSFSR), the republic in which the combine is located; and (3) the U.S.S.R. as a whole.

The results indicated an excess of cancer mortality among the nickel workers. The excess was consistent among men and women and by age group. The workers' lung cancer death rate "exceeded that of the urban population by 180 percent," and appeared to be highest in the roasting-reduction shop and the cobalt shop. An excess of stomach cancer deaths among all of the workers combined was statistically significant among those aged 50 and older.

The 1973 report presented results of a similar study of four nickel plants. Pyrometallurgical and electrolytic processes were used. Apparently, two of the plants processed oxide ores and two processed sulfide ores. The English translation uses the term "oxided nickel ores" throughout. The authors concluded that cancer mortality from 1955 to 1967 was higher among nickel plant workers than in the urban population in the same geographic area for each nickel plant. In particular, lung and stomach cancer deaths were seen in excess, as were deaths due to sarcomas (especially of the hip, lung, and intestine).

For both the 1970 and 1973 reports, it is difficult to evaluate the findings due to the lack of information on cohort definition, follow-up, and analytical methods. The authors did not state whether a person-years method was used, but the numbers shown suggest that it was not; thus, the results cannot be interpreted reliably.

8.1.9 Oak Ridge Nuclear Facilities, Tennessee (U.S.A.)

Several studies of the possible carcinogenicity of nickel have been conducted utilizing data on employees of the Oak Ridge nuclear facilities.

One set of studies (Section 8.1.9.1: Godbold and Tompkins, 1979; Cragle et al., 1983, unpublished; 1984) focused on workers exposed or not exposed to metallic nickel powder, which also may have been accompanied by exposure to nickel oxides when the fine metal powder was exposed to air. These studies included 814 men who worked in the "barrier" manufacture department of the Oak Ridge Gaseous Diffusion Plant (ORGDP), and nearly 8,000 men who were employed at the ORGDP but not in barrier manufacture.

Another set of studies (Section 8.1.9.2: Polednak, 1981; Gibson, 1982) focused on welders exposed or not exposed to nickel oxide through the welding of nickel-alloy pipes. These studies included 536 welders who worked at the ORGDP, where nickel-alloy pipes were welded, and 523 welders who worked at two other Oak Ridge plants and whose exposure to nickel oxide was much less.

It is unclear whether there is any overlap of study subjects in the barrier manufacture and the welding studies. The possible impact of such an overlap, if any, will be discussed in the summary of the Polednak (1981) paper.

8.1.9.1 Oak Ridge Gaseous Diffusion Plant, Metallic Nickel Powder Exposure.

Metallic nickel, in the form of a finely divided, very pure powder, is used in the manufacture of a porous "barrier" employed in the isotopic enrichment of uranium by gaseous diffusion. Production of barrier from metallic nickel is carried out at the Oak Ridge Gaseous Diffusion Plant (ORGDP) of Union Carbide's Nuclear Division in Oak Ridge, Tennessee. A brief description of the history of barrier production at this plant and the population under study will be followed by a summary of the methods and results reported by Godbold and Tompkins (1979) and by Cragle et al. (1983, unpublished; 1984).

Workers who manufactured the barrier were studied in regard to two factors: (1) the National Institute for Occupational Safety and Health (1977a) position that metallic nickel is a suspect carcinogen because fine dusts of nickel may oxidize and be inhaled as nickel oxides by workers; and (2) the equivocal evidence on the carcinogenicity of airborne metallic nickel per se.

The manufacture of barrier at ORGDP began in January 1948. By the end of 1972, 980 workers had worked in the barrier plant for at least one day. Because 852/980 (87 percent) of the workers had had some experience in the barrier plant by the end of 1953, and because setting the cut-off date for the study cohort at 1953 allowed at least 19 years of follow-up for each worker in the study, only those employees who had worked at sometime between January 1, 1948 and December 31, 1953 were included in the study. The study cohort of exposed "barrier" workers was limited to the 814 males who had worked in the barrier plant for at least one day in the specified time period. The cohort did not include females because so few (38) were available for study.

The duration of work in the barrier plant ranged from 3 days to 25 years (mean = 5.3 years; median = 3.8 years). Six men worked less than 1 month; 65 worked 1 to 6 months; and a total of 161 (20 percent) worked for 1 year or less. The short duration of exposure of such a large proportion of the cohort could have been used in the analysis to illuminate the possible relationships between exposure and mortality; but, as will be discussed, neither report took the duration of exposure into account.

An "unexposed" cohort was also studied. This cohort comprised white males who had worked at least one day at ORGDP between January 1, 1948 and December 31, 1953 and who had no record of having worked in the barrier plant or of having had other exposure to nickel at ORGDP. The exact number of such workers was not reported consistently in the two papers. Godbold and Tompkins (1979) studied a 25 percent systematic sample of these workers; they studied 1,600 workers, which implies that the group originally comprised 6,400 men. On the other hand, Cragle et al. (1983, unpublished; 1984) studied 7,552 workers, a number in excess of the 6,400 estimated from the Godbold and Tompkins report.

In both studies, vital status was ascertained through the Social Security Administration, and underlying causes of death were determined from death certificates. Godbold and Tompkins followed workers through December 31, 1972; Cragle et al. continued through December 31, 1977. Godbold and Tompkins coded causes of death according to the ICDA revision in effect at the time of death; Cragle et al. used one system throughout, the Eighth Revision of the ICDA.

8.1.9.1.1 Godbold and Tompkins (1979). In this study, 814 barrier workers and 1,600 "control" workers with at least one day of employment at ORGDP were followed for mortality through December 31, 1972. Death certificates were obtained for all but one of the 85 deaths among barrier workers, and for all but 11 of the 273 deaths among unexposed workers; in the analysis, the remaining deaths were distributed among the known causes of death in proportion to the distribution of those causes among the 262 with known causes.

Analysis of each cohort (barrier and unexposed workers) for each underlying cause of death was performed by comparing the observed numbers of deaths with the numbers expected based on age group-, calendar time-, and cause-specific rates for U.S. white males. An SMR and its 95 percent confidence interval was presented for all-cause mortality. For cause-specific mortality, only the observed and expected numbers of deaths were shown for most causes.

The results showed that each cohort experienced lower total mortality than expected, based on overall statistics for white males in the U.S. The SMR for the barrier workers was 75 (95 percent confidence interval of 60 to 94), and for the unexposed cohort was 84 (74 to 94). These are not unusual findings in occupational studies, in which such results are often attributed to the "healthy-worker effect." However, since this effect should operate less strongly in cohorts in which only a small proportion of workers are still employed at the end of the study, the healthy-worker effect may not fully explain the lower-than-expected mortality in the ORGDP cohorts. (Of the 814 barrier workers, only 69 were still employed at the plant in 1974, and of the 1,600 unexposed workers, only 203 were still employed.) Godbold and Tompkins suggested that three factors may be operating: (1) the healthy-worker effect, (2) underreporting of deaths by the Social Security Administration, and (3) the active occupational health program at ORGDP. Other possible factors, such as a lower proportion of cigarette smokers among ORGDP employees than in U.S. white males overall, were not explored. No smoking data were collected before 1955, but smoking information was presented for more than half of the barrier workers and for nearly half of the unexposed workers.

The barrier workers had only 3 respiratory cancer deaths, while 6.68 were expected (SMR = 45, 95 percent confidence interval of 9 to 131). Unexposed workers had 21.85 respiratory cancer deaths (note that the fractional number is a result of the allocation of deaths of unknown cause) compared to 19.42 expected (SMR = 113, 95 percent confidence interval of 71 to 171). All of the respiratory system cancer deaths were due to lung cancer. No nasal cancer deaths were seen. The deficit among barrier workers does not appear to have been due entirely to the relatively decreased proportion of smokers in that cohort. It is not advisable to compare the SMRs from the two cohorts directly because the age distributions and thus the person-year distributions differ; according to Cragle et al. (1983, unpublished; 1984), the barrier cohort was somewhat younger than the unexposed cohort.

The barrier workers showed some excess of genitourinary organ cancer deaths (SMR = 161, O/E = 3/1.86), while unexposed workers did not (SMR = 63, O/E = 4.16/6.64). Data were not presented for specific genitourinary sites. The barrier workers had a statistically significant deficit of deaths due to diseases of the circulatory system (SMR = 65, 95 percent confidence interval of 24 to

90). The SMR for this cause among unexposed workers was 89 (no confidence interval given). Godbold and Tompkins suggested that the deficiency in this cause of death may be due to the "extensive program in occupational medicine" at the ORGDP. Both cohorts also experienced smaller than expected numbers of deaths due to diseases of the digestive system: SMR = 44 among barrier workers (O/E = 3/6.90); SMR = 6 among unexposed workers (O/E = 1.04/18.07). The authors offered no explanation for this finding.

Overall, this report showed no evidence of an increase in risk of death due to respiratory cancer among workers exposed to metallic nickel dust in a barrier plant. The length of follow-up was at least 19 years for each member of the exposed and unexposed cohorts. The degree of exposure of the nickel workers in the barrier plant appears to have been "substantial." The authors stated that "it can be assumed that all of the (barrier) workers were exposed to levels greater than the recommended NIOSH standard of 0.015 mg/m^3 during most of the work day." Thus it would appear that, for this length of follow-up and this level of airborne nickel dust, metallic nickel exposure in this cohort was not associated with respiratory malignancy deaths. The study, however, did not take into account either the broad variability in duration of exposure or the variation in airborne nickel level in areas of the barrier plant, and thereby may have obscured a possible association.

8.1.9.1.2 Cragle et al. (1983, unpublished; 1984). In these reports, the data set presented by Godbold and Tompkins (1979) was extended and new analyses were performed. Since the 1983 and 1984 versions were very similar, they will be discussed together here. The same cohort of 814 exposed barrier workers was studied, while the 25 percent sample of the unexposed workers was expanded to include all of the 7,552 white male workers. The mortality follow-up time was extended an additional five years, to December 31, 1977. All of the underlying causes of death were coded to the Eighth Revision of the ICDA. Follow-up of the cohorts was slightly less complete up to 1977, as compared to the follow-up to 1972 by Godbold and Tompkins. The vital status of 90 percent of the 814 barrier workers and of 93 percent of the unexposed workers was ascertained. Of 137 deaths among barrier workers and 1,920 deaths among the other workers, death certificates were obtained for 97 percent.

The results of two methods of analysis were presented: SMR analysis, with 95 percent confidence intervals, based on age- and calendar year-specific rates among U.S. white males; and directly standardized death rates for several selected causes of death, based on the entire combined ORGDP data set as the standard population. While the latter analysis provides the ability to directly compare the rates in the two cohorts, the use of the combined cohorts instead of the unexposed cohort as the standard population may tend to minimize any differences between the two cohorts.

The results for selected causes of death as indirectly standardized mortality ratios are shown in Table 8-8. Among nickel-exposed workers, the suggestion of lower SMRs for all-cause mortality, respiratory diseases, and diseases of the circulatory system among nickel workers, observed by Godbold and Tompkins (1979), continued to be observed with the extended follow-up time. Deaths from cancer of the respiratory system continued to be fewer than expected among nickel workers (SMR = 59, 95 percent confidence interval of 21 to 128, with 6 observed deaths). The directly adjusted death rate for respiratory cancer was lower among nickel workers as compared to other, unexposed workers (0.39 versus 0.81 per 1,000 person-years).

The SMR for death from cancer of the buccal cavity and pharynx was 292 among nickel workers, with a wide confidence interval including 100 (59 to 845), according to Table 2 in both the 1983 and 1984 versions of the report. A statistically significant deficit of this cancer was observed among the unexposed workers: SMR = 23, 95 percent confidence interval of 5 to 67. Additional evidence of a difference between the groups is seen when directly standardized death rates are compared: the adjusted mortality rate for this cause among nickel workers was 0.32 per 1,000 person-years (95 percent confidence interval of 0.0 to 0.69), while the similarly adjusted rate among unexposed workers was 0.02 per 1,000 person-years (95 percent confidence interval of 0.0 to 0.03). Thus, the rate among exposed workers was higher than the upper limit of the 95 percent confidence interval for the rate in unexposed workers. It should be noted that these are head and neck tumors, a finding consistent with the site of other tumors associated with nickel.

8.1.9.2 Oak Ridge Plants, Primarily Nickel Oxide Exposure to Welders. At one plant of the Oak Ridge nuclear facilities (the Oak Ridge Gaseous Diffusion Plant, known as K-25), nickel-alloy pipes "are a major constituent of the plant." Welders assigned to K-25 are thought to have been exposed to higher levels of airborne nickel and nickel oxide than welders at either of two other Oak Ridge plants (X-10 and Y-12). Industrial hygiene data substantiated this difference in exposure levels. The major air and urinary contaminants at the

TABLE 8-8. STANDARDIZED MORTALITY RATIOS (SMRs)[a] FOR SELECTED CAUSES OF DEATH AMONG NICKEL WORKERS AND UNEXPOSED WORKERS

	Nickel workers (n = 814)		Unexposed workers (n = 7552)	
Cause of death	No.	SMR (confidence interval)[b]	No.	SMR (confidence interval)[b]
All causes	137	92 (77-109)	1920	98 (94-102)
Disease of the circulatory system	56	78 (59-102)	984	98 (92-104)
Disease of the digestive system	6	68 (25-149)	68	65 (51-83)
Respiratory disease	6	80 (29-174)	101	93 (76-114)
Malignant neoplasms	29	100 (67-143)	352	92 (83-102)
Cancers:				
Buccal cavity and pharynx	3	292 (59-854)	3	23 (5-67)
Digestive organs and peritoneum	8	104 (45-205)	79	73 (58-91)
Respiratory system	6	59 (21-128)	151	116 (98-136)
Prostate	1	92 (1-512)	21	104 (65-159)
Kidney	0	- (0-465)	12	121 (62-211)
All lymphopoietic	4	123 (33-316)	41	105 (75-142)

[a] Expected deaths based on overall U.S. white males.
[b] 95% confidence interval assuming that the observed deaths follow the Poisson distribution.

Source: Adapted from Cragle et al. (1983, unpublished).

K-25 plant were nickel and fluoride, while at the other plants they were iron and chromium. It should be noted that K-25 welders may also have worked at the other plants.

Polednak (1981) focused on this difference in nickel exposure levels in a mortality study of welders at Oak Ridge. Polednak's study design and results are described below, as well as a published comment on the study by Gibson (1982).

All of the white male welders employed at the Oak Ridge nuclear facilities between 1943 and January 1, 1974 (n = 1,059) were followed for mortality through January 1, 1974. Ninety-three percent of the cohort were followed for at least 13 years. Vital status was ascertained through the Social Security Administration and current employment status; vital status was unknown for 83 of 1,059 men, who were then assumed to be alive at the end of the follow-up period. Death certificates were obtained for all but 7 of the 173 known deaths. SMRs based on U.S. white male mortality, with 95 percent confidence intervals, were calculated.

The 1,059 welders were classified as to the plant at which they had been employed. Five hundred thirty-six welders had worked at K-25, the plant at which higher levels of nickel exposure had occurred, and 523 had worked at the X-10 or Y-12 plant. The author did not comment on the possibility that a man may have worked at K-25 and also X-10 or Y-12, or how such an individual might be classified in the analysis.

The K-25 welders and the other welders were similar in age at entry (mean age, 31.5 versus 33.8 years); mean year of entry (1949.0 versus 1951.3); and person-years of follow-up (12,553 versus 11,121). Data are not given regarding duration of employment. The scanty data on smoking habits suggest that the proportion of K-25 welders who were heavy smokers was lower than among other welders and similar to overall U.S. rates; therefore, any increased respiratory cancer mortality among K-25 welders would be unlikely to be due to an excess of cigarette smokers.

Results of the analysis among the entire group of 1,059 welders showed a nonsignificant increase in lung cancer deaths: SMR = 150, with 17 deaths observed and 11.37 expected; 95 percent confidence interval of 87 to 240. No deaths due to nasal sinus cancer were seen. A nonsignificant increase in deaths due to diseases of the respiratory system was reported (SMR = 133) and was attributed mainly to emphysema.

In the separate analyses of K-25 and other welders, the only statistically significant SMR was that seen among K-25 welders for deaths due to diseases of the circulatory system: SMR = 70, 95 percent confidence interval of 49 to 98. Nonsignificant increases were observed for lung cancer deaths among K-25 welders (SMR = 124) and other welders (SMR = 175), and for diseases of the respiratory system among other welders (SMR = 167) but not K-25 welders (SMR = 101).

To allow for a biologically plausible latency period in the analysis of respiratory cancer deaths, an analysis was performed excluding men with fewer than 15 years from date of hire to date of death or end of follow-up. Among 922 welders with at least 15 years of follow-up, respiratory cancer showed an SMR of 176 (O/E = 16/9.10). Among the 478 welders at the K-25 plant with at least 15 years of follow-up, the respiratory cancer SMR was 126 (O/E = 6/4.76). The 95 percent confidence intervals were not shown.

Additional subgroup analysis considering length of employment as a welder showed a nonsignificant excess of lung cancer deaths among K-25 welders with at least 50 weeks of exposure (SMR = 175), while the SMR among all welders with at least 50 weeks of exposure was 121. However, methodological considerations, as well as the observation pointed out by Gibson (1982) that respiratory cancer among the K-25 welders was the single cause of death presented in which the SMR increases with length of employment, would suggest that a new analysis of this subgroup should be carried out.

The interpretation of the findings of this study is subject to several problems. Most importantly, welders were exposed to a variety of potentially harmful agents, some of which are known to be carcinogenic. The K-25 welders included many men who had very short periods of exposure in the K-25 plant, and thus any excess risk due to nickel exposure may have been obscured. In addition, the possible overlap in study subjects between the Cragle et al. (1983, unpublished; 1984) study, which included 1,600 workers in "barrier" manufacture at the Oak Ridge Gaseous Diffusion Plant (ORGDP) and the Polednak (1981) study's 523 welders at the K-25 plant, which seems to be the ORGDP itself, remains to be clarified. If the K-25 welders worked in the location where "barrier" was being manufactured, they would have been exposed to pure metallic nickel powder as well as the nickel oxide which resulted from welding nickel-alloy pipes. Any increase in lung cancer deaths could be attributed, in part, to the combined exposures to both the nickel oxide and the pure metal powder, and not just to the welding exposure itself.

In summary, this study does not provide evidence of an association between nickel oxide exposure among welders at the K-25 plant and lung cancer. However, the SMR of 176 for respiratory cancer among welders with at least 15 years of follow-up was of borderline statistical significance, as calculated by Wong et al. (1983, unpublished).

8.1.10 Nickel-Using Industries

A number of recent reports have been issued on the risks among workers employed in industries which use nickel. The industries studied include die-casting and electroplating, metal polishing and plating, nickel alloy manufacturing, and nickel-cadmium battery manufacturing. The predominant nickel species in these studies are metallic nickel dust or powder and nickel oxide. In several of the studies, there was concurrent exposure to other metals, a factor that poses problems in establishing associations between cancer risks and nickel exposure. This aspect of the present review of the literature is not comprehensive, but is included to illustrate the possible risks of exposures to nickel in industries other than mining and refining.

8.1.10.1 Die-casting and Electroplating Workers (Scandinavia). A nested case-control study of deaths among workers in a die-casting and electroplating plant that opened in the 1950s was carried out by Silverstein et al., 1981. Deaths occurring between January 1, 1974 and December 31, 1978 were studied. In the 1950s and 1960s, the major operations of the plant were zinc alloy die-casting; buffing, polishing and metal cleaning of zinc and steel parts; and electroplating with copper, nickel, and chrome. Specific exposures at the plant were not precisely characterized. A preliminary proportionate mortality ratio (PMR) study of 238 deaths occurring among workers employed at least ten years showed an excess PMR for lung cancer among both males and females. This was the only cause of death which showed a statistically significant excess PMR. The authors subsequently initiated a nested case-control study of the 28 white male and 10 white female lung cancer deaths. Two age- and sex-matched controls were selected for each case from among those who died of nonmalignant cardiovascular disease. Cases and controls were compared for length of employment in individual departments. Work histories of cases and controls were abstracted from company personnel records.

Odds ratios were estimated for work in 14 different departments. For males in three departments (identified as Departments 5, 8, and 38), the odds ratio increased with length of time worked in those departments. The trend was most significant for Department 5, in which the major activity was die-casting and plating. According to the authors, the case-control study lacked internal consistency. They stated that Department 6 for example, was probably the most similar to Department 5 in the nature of chemical exposures in the 1950s and the 1960s, but that there was no increase in trend of relative risk among white males in that department.

In summary, this study suggests that the risk of lung cancer mortality is associated with work in the plating and die-casting plant. However, because workers were exposed to a number of possible carcinogens in addition to nickel, and because definitive information on exposure is missing, it is impossible to state whether the risk of lung cancer resulted from nickel exposure. This study, therefore, provides no definitive information on the risk of lung cancer either from nickel exposure or from specific nickel species.

8.1.10.2 Metal Polishing and Plating Workers (U.S.A.). Workers engaged in the polishing, electroplating, and coating of metals are exposed not only to metals (e.g., nickel, chromium, copper, iron; lead, zinc) but also to acids, alkalies, and solvents. An exploratory study of cancer mortality among these workers was reported by Blair (1980).

In this proportionate mortality study, 1,709 deaths among members of the Metal Polishers, Buffers, Platers, and Allied Workers International Union were studied. The deaths were ascertained through obituary notices in the union's journal and thus were limited to workers who were in good standing in the union at the time of death. These deaths occurred between 1951 and 1969. Death certificates were obtained for 1,445 (85 percent), and causes of death were coded according to the Eighth Revision of the ICDA. Analyses were restricted to the 1,292 white males for whom death certificates were obtained. PMRs were calculated based on five-year age and calendar time-specific deaths among U.S. white males.

Of the 1,292 deaths, 53 percent occurred among workers who were younger than 66 years of age. This disproportionately young distribution of age at death is probably an artifact of the method of ascertainment and the fact that most decedents were active members of the union at the time of death. When interpreting the results of the analyses, it should be kept in mind that deaths among retired and older workers thus were underrepresented relative to all workers in the industry. However, the PMR does take into account the ages of the decedents whose deaths were counted.

A significantly increased PMR was observed for esophageal cancer (10 observed versus 5.4 expected, PMR = 185, $p < 0.05$) and primary liver cancer (5 observed versus 1.8 expected, PMR = 278, $p < 0.05$). Nonsignificant excesses were seen of deaths from cancer of the buccal cavity and pharynx, rectum, pancreas, and larynx, as well as from non-Hodgkin's lymphoma and Hodgkin's disease. No excess of lung cancer deaths was seen (62 observed versus 58.7 expected). No nasal cancer deaths were ascertained, while 0.6 were expected.

There was a statistically significant excess of deaths from all cancers among those who had died at ages 66 and older; 111 cancer deaths were observed compared to 92.6 expected, PMR = 120, $p < 0.05$; among deaths at 65 or younger, 133 cancer deaths were observed compared to 131.2 expected, PMR = 101, not statistically significant ($p > 0.05$). This finding is not surprising in view of the latent period between exposure and death from cancer. The observation that the excess of esophageal and primary liver cancer (as well as cancers of the colon, rectum, pancreas, prostate, and bladder) was stronger among deaths occurring at age 66 and older, combined with the fact that deaths among men who had left the industry probably were underascertained because this study was limited to active union members, suggests that the study result may not be generalized to all workers in the industry. Further and more definitive studies using a cohort design should be carried out.

On the other hand, the slight excess of deaths due to cancer of the buccal cavity and pharynx, non-Hodgkin's lymphoma, and Hodgkin's disease among deaths occurring at age 65 or younger suggests that these causes should also be given further attention among workers in this industry.

8.1.10.3 Nickel Alloy Manufacturing Workers (Hereford, England). Exposure to metallic nickel and nickel oxide, but not nickel subsulfide, occurs in the manufacture of nickel alloys from raw materials. Other exposures include chrome, iron, copper, cobalt, and molybdenum. A cohort mortality study of men employed at a nickel alloy manufacturing plant in Hereford, England, was reported by Cox et al. (1981).

Industrial hygiene measurements of specific airborne metals, including nickel, in the various operating areas of the plant were made systematically since 1975, and the data were summarized in Table 2 of the study. The average concentration of airborne nickel between 1975 and 1980 ranged from 0.84 mg/m^3 in the melting, fettling, and pickling areas, to 0.04 mg/m^3 in the process stock handling and distribution and warehouse areas. Some data were presented on the state in which the airborne nickel was found in specific areas of the plant, ranging from 14 percent metallic nickel in the welding section to 50 percent in the fettling area, and from 14 percent water-soluble nickel in the melting department to 49 percent in the extrusion section.

A cohort was identified of 1,925 men who had worked in the operating areas of the plant for at least five years, excluding breaks, from the opening of the plant in May 1953 through the end of March 1978. The men were classified into six occupational categories corresponding to the five areas with airborne nickel measurements reported in Table 2 of the study, plus a sixth category for men who had been transferred to the staff from other occupations. One subgroup analysis considered men who were "likely to have had more than average exposure to atmospheric nickel" (Cox et al., 1981) i.e., those who fell into either of the two occupational categories with the highest total dust exposure (mg/m^3). There is no discussion of the possibility that exclusion of the men who had transferred from other occupations to the staff might have excluded men who were experiencing health effects of workplace exposure, and thus might have decreased the number of pertinent deaths in the subgroup analyzed.

The cohort was followed for mortality through April 1, 1978, with a potential range of follow-up time from 0 to 20 years after satisfying the cohort criterion of a minimum of 5 years of employment. No data were given on the distribution of follow-up time or the proportion of the cohort with at least 20 years at risk of cancer death in the follow-up period. Of the 1,925 men, 22 were not traced and 22 had emigrated; these were withdrawn from the person-years calculation at the time of last contact or emigration.

One hundred seventeen deaths were ascertained, and the underlying causes of death were coded according to the Eighth Revision of the ICDA. To calculate SMRs, expected numbers of deaths were obtained using age- and calendar time-specific rates for men in England and Wales; and a correction for geographical location was made "by multiplying by the standardized mortality ratios for the urban areas of the county in which the factory was located" using mortality ratios for men 15 to 64 years of age in 1969 to 1973. It should be noted that this correction for geographical area constitutes a methodologic strength. However, if the working population of the plant of interest constitutes a large proportion of the geographic area's population, the effect of such a step could be to make the expected numbers of deaths more like the observed numbers of deaths for the SMRs ultimately obtained, bringing the "corrected" SMRs closer to 100.

Results showed an SMR for overall mortality of 74 when calculated by the usual method, and 81 when corrected for geographical area. No excess of cancer, lung cancer, or other respiratory disease deaths was seen. No deaths due to nasal sinus cancer were ascertained, while 15 deaths were due to lung cancer and 1 to laryngeal cancer (SMR not given). Despite the very low numbers of deaths, subgroup analyses were performed. These showed no excess of deaths from specific causes, but the power of the analysis to detect an excess was small. The corrected SMR for lung cancer among men with above average exposure to airborne nickel was 124.

In summary, while this study provided no evidence of excess mortality risk among men exposed to metallic nickel and nickel oxide, the study was not designed to provide a powerful test of the hypothesis. The sample size was not large, and the follow-up time was relatively short.

8.1.10.4 High-Nickel Alloy Plant Workers (U.S.A). Redmond et al. (1983, unpublished; 1984) completed a mortality follow-up study of 28,261 workers from 12 high-nickel alloy plants. The study group included workers employed for at least one year in a nickel alloy plant, who had worked for at least one month between 1956 and 1960. Workers employed strictly as administrative office personnel, such as secretaries, were excluded. The calendar time criteria for defining most of the cohort, i.e., 1956 to 1960, was different for four of the plants, for which the calendar periods were 1962 to 1966, 1967, 1956 to 1966, and 1961. Ninety percent of the cohort was male, and 92.5 percent was white. The follow-up period was from 1956 to 1977, for a total of 21 years. Deaths were ascertained through the Social Security Administration and company records. Three percent were lost to follow-up. During the follow-up period, 292 lung cancer, 9 laryngeal cancer, 2 nasal cancer, and 25 kidney cancer cases were identified from death certificates.

Exposure was defined by category of work and length of employment. All job titles were classified into one of 11 work areas. Some data on exposure to metals and particulates by work area were noted, and are summarized in Table 8-9. The predominant nickel species to which the workers were exposed appear to have been nickel dust and oxide, although the authors' descriptions did not clearly spell out the associations between species and work setting.

TABLE 8-9. POSSIBLE NICKEL EXPOSURES AND LEVELS OF EXPOSURE BY CATEGORY OF WORK IN THE HIGH-NICKEL ALLOY INDUSTRY

Category of work	Possible Ni species	Exposure level (mg Ni/m^3) Range	Average
Cold working	Ni dust	0.001-2.3	0.064
Hot working	Ni dust Ni oxide	0.001-4.2	0.111
Melting	Ni dust Ni oxide	0.001-4.4	0.083
Grinding	Ni dust Ni oxide	0.001-2.3	0.298
Allocated services	Many non-Ni exposures	0.001-0.350	0.071
Foundry	Ni dust	0.004-0.900	0.098
Powder metallurgy	Ni powder	0.001-60.0	1.5
Administrative	------	------	------
Pickling and cleaning	------	------	------

Source: Adapted from Redmond et al. (1983, unpublished).

The levels of exposure to nickel were relatively low, ranging from an average low of 0.064 mg/m^3 in the cold working area to a high of 1.5 mg/m^3 in the powder metallurgy area.

When analyses were done by work area, the authors did not classify individuals into mutually exclusive categories. If a worker had ever been employed in a work area, presumably for at least one day, that individual was considered in the analysis for that work area. An individual could therefore have contributed his person-years to several different work categories. As a result, there is some lack of independence in the SMRs by work area. Twenty percent of the work force had been employed for 20 or more years. SMRs were calculated using race- sex-, age-, and time-specific U.S. rates for all diseases. Lung, laryngeal, kidney, and nasal cancers were the specific focus of this study. Analyses were presented by race, sex, plant, number of years exposed (length of employment), and work area.

The results of this study were predominantly negative. The few statistically significant SMRs were relatively low. The SMR for all males and females did not show a statistically significant excess risk for the four tumor sites of interest. SMRs for lung cancer by plant for white males, the largest group, ranged from 37.7 to 190.8. However, none were statistically significant. The other three tumors were too infrequent to analyze by plant. SMRs for lung, laryngeal, and kidney cancers were estimated by length of employment (less than 20 years versus 20 or more years). The only significant excess risk was shown for lung cancer (SMR = 118, $p < 0.05$) among white males working less than 20 years, but not among those with 20 or more years of employment (SMR = 100). No dose-response relationship was shown using length of employment as a measure of dose. However, the excess risk could reflect differences in the jobs held by short- and long-term workers, e.g., unskilled versus skilled labor. Analyses were also done by work area for the same three tumors. The following statistically significant excess risks were found: lung cancer among white males in Allocated Services (SMR = 120, $p < 0.01$), and kidney cancer among white males in the cold working area (SMR = 263.4, $p < 0.05$).

SMRs were estimated for subgroups defined by work area, number of years employed (less than 5 years versus 5 or more years), and number of years since first employment (less than 15 years versus 15 or more years). The only statistically significant SMRs were found for lung cancer in Allocated Services for those working 5 or more years, both among those with less than 15 years (SMR = 142.8, $p < 0.05$) and those with 15 or more years (SMR = 124.3, $p < 0.01$) after first employment; for lung cancer in the melting area, for those with less than 5 years' exposure and 15 or more years after first employment (SMR = 172, $p < 0.05$); for kidney cancer in the melting area, for those working less than 5 years and with less than 15 years since first employment (SMR = 555.6, $p < 0.05$); and for kidney cancer among foundry workers with 5 or more years' exposure and 15 or more years since first exposure (SMR = 769.2, $p < 0.05$).

The statistically significant SMRs for lung cancer among the Allocated Service workers occurred for those employed longer, and are based on a large number of observed cases (36 and 161, respectively). On the other hand, the statistically significant SMR for lung cancer in the melting area is for short-term workers, and is inconclusive. In addition, the SMRs for kidney cancer are based on a very small number of observed cases (three and two, respectively), and are only significant for those with shorter, but not longer, term employment. The SMRs for kidney cancer may be due to chance, especially given the large number of SMRs estimated.

The excess lung cancer risk in Allocated Services (includes "pattern and die, maintenance, guards and janitors, and other") appears to have been concentrated among white male maintenance workers. However, the data presented do not enable a conclusion to be made about the specific exposures which may be associated with the excess risk.

The results of this study were largely negative, with the exception of the few statistically significant SMRs noted above. The predominant nickel species appears to have been nickel dust or powder, and nickel oxide. While there was some discussion of nickel exposure by work area, there was no discussion of the species-specific exposure by job category. As a result, exposure groups defined by work area may have been quite heterogeneous. Nonetheless, the great number of SMRs that were derived must be considered when evaluating the relatively few statistically significant SMRs in this study. In addition, the absence of a coherent relationship among significant SMRs suggests the possibility of either chance associations or that exposures other than nickel may have been involved. The latter may be of special significance given the variety of exposures in the plant including, in the Allocated Services area, potential exposure to welding fumes, solvents, lubricants, cleaning materials, resins, and other chemicals. Finally, the assignment of individuals to exposure categories on the basis of "ever working" in particular areas is likely to have significantly reduced the findings as to risks associated with specific types of work, because of the potentially large number of short-term workers in these categories.

8.1.10.5 Nickel-Chromium Alloy Foundry Workers (U.S.A). Landis and Cornell (1981, unpublished) and Cornell and Landis (1984) conducted a proportionate mortality ratio (PMR) study of 992 male deaths (out of 1,018 total deaths) among nickel-chromium alloy workers from 26 plants. Of these plants, 6 had opened before 1945, and 20 had opened after 1945. The target population included both current and retired workers. The period of death ascertainment was between 1968 and 1979. Identification of deaths and information on exposure status were provided by the foundries; none of the primary data collection was done by the authors. The method of data collection does not provide any assurance of completeness of data collection, reliability of exposure classifications, quality of information, or comparability among the 26 plants.

Individuals were considered to have been exposed if they had worked in any operation which had potential nickel-chromium exposure. "All foundry workers in a given foundry were presumed to be exposed if they worked during the period after the initial year of nickel-chromium production for that foundry." No information was provided regarding the organization of the foundries. It is possible that any given foundry is divided into a number of departments, each with different exposures. It appears that a worker was considered unexposed if he had been employed during a time when nickel-chromium production was not in operation at that foundry; thus, the unexposed group may have worked at different calendar times than the exposed group.

Personal monitoring data on nickel and chromium levels from six plants were obtained. Since these were recent measures, it is likely that they were lower than would have been obtained for past exposures. For nickel, the arithmetic means for different areas in the plant ranged from 14 $\mu g/m^3$ to 233 $\mu g/m^3$. Because of the relatively low ambient levels of both nickel and chromium, and the likelihood of short-term employment in the foundry, it is likely that a large proportion of the exposed group had relatively low exposures.

Cause-of-death distributions for all U.S. male deaths in 1974 by five-year age subgroups and race were used to compute expected values for the standardized PMRs. The year 1974 was selected as a standard because it was the median year of death. Although the authors stated that the distribution of deaths may have changed over the 12-year period from 1968 to 1979, they provided no justification for using the single year, 1974, in order to standardize the PMRs. It would have been simpler and more straightforward for the authors to have used calendar year- and age-specific ratios to derive the expected values. Standardized PMRs (SPMRs) were provided separately on those dying before age 65, and at age 65 and older. For those dying before age 65, the SPMR for lung cancer was 0.8, which is not statistically significant. The SPMR for kidney and ureter cancer was in slight excess (SPMR = 110), but was not statistically significant. The only statistically significant SPMR was for diseases of the respiratory system, at 168 ($p < 0.05$). Workers dying at age 65 or older had a statistically significant SPMR for lung cancer of 148 ($p < 0.05$). This subgroup also showed an SPMR greater than 1 for diseases of the respiratory system; however, it was not statistically significant (SPMR = 123). The authors did not standardize the mortality ratios by length of employment for age or race.

Therefore, it is not possible to make any inference about the relationship between length of employment and the PMR for respiratory cancer.

In the 1981 paper the authors directly compare the proportionate mortalities of 851 exposed deaths with 139 unexposed deaths. The proportionate mortalities were not standardized to some external population. Age may be a confounder in this analysis since it appears from the definition of exposure that the exposed and unexposed workers were likely to have been employed at different times and may have had different age distributions.

The authors (1981) showed that among exposed workers there was a direct relationship between the proportion of deaths due to lung cancer and the length of employment. However, the proportionate mortalities for the groups defined by length of employment were not standardized for age. Nonetheless, the authors discounted the relationship by noting that the lung cancer proportionate mortality in unexposed workers was almost equivalent to that found among the exposed workers with the greatest length of employment. Again, as noted above, this is probably not a valid comparison for two reasons. First, given the definition of exposure, it is likely that the unexposed workers were employed at a different time than the exposed group. Second, these ratios are not adjusted for age, and as a result, the comparison could be confounded by age. What is striking is the apparent dose-response relationship among exposed workers. To test for a trend by length of employment while controlling for age, the authors distributed the 60 exposed cases among 12 categories defined by length of employment (4 groups) and age (3 age-at-death groups). The test for trend with length of employment was not statistically significant. However, since 60 cases were distributed over 12 categories, the statistical power of the data was severely limited.

The authors noted that "it can be concluded that the respiratory cancer rates do not show a significant increase across length of exposure subgroups after adjustment for age, race, and length of employment. Thus, the apparent trend in respiratory cancer rates...may be associated with either increasing age or length of foundry employment, regardless of the exposure to nickel-chromium." This conclusion does not seem justified given the problems discussed above, and cannot be evaluated without more details on the distribution of deaths by age and year of employment. The authors noted that "the exposed and unexposed subgroups exhibit similar increases in respiratory cancer with increasing length of employment." In fact, the patterns seem to be different. The exposed workers showed an increasing ratio with increasing length of employment, and the unexposed workers showed a somewhat decreasing ratio with increasing length of employment.

In their conclusion, the authors stated that "workers and retirees from the foundry industry . . . do not experience a significantly different proportion of deaths from cancer, and specifically from cancer of the lung and cancer of the kidney, than would be expected from the age-specific proportional mortality patterns observed in the United States as a whole." The analysis in this paper is inadequate to support this statement. In fact, the evidence suggests that the contrary may be true, at least in the case of lung cancer, for which a statistically significant PMR was shown, and for which the PMR (not standardized) showed an association with increasing length of employment. In summary, this study should not be considered as evidence of no risk from nickel-chromium exposure in the alloy foundry industry. Given the concurrent exposure to both nickel and chromium, however, it is impossible to determine if nickel alone could account for the noted patterns of death.

The 1984 published paper is an abbreviated version of the 1981 unpublished document and does not contain the same details regarding either the data collection methods or analysis. In the 1984 paper the authors note that "the increase in respiratory cancer percentages is not statistically significant across length of exposure subgroups after adjustment for age, race, and length of employment." However, no data are provided to support this statement. In addition, it is possible that in adjusting for length of employment, the association between length of exposure and respiratory cancer percentages could be eliminated, especially if length of employment and exposure are highly correlated.

8.1.10.6 Stainless Steel Production and Manufacturing Workers (U.S.A.).

Cornell (1979, unpublished; 1984) conducted a PMR study of 4,882 deaths among workers in 12 stainless steel plants. Deaths were identified from records on retirees eligible for insurance benefits and from records on active workers. All of the deaths except one occurred between 1973 and 1977; one death occurred in 1962. Presumably, deaths of "active workers" were deaths that occurred on the job. A total of 4,487 deaths were of white males, the only group large enough for serious considerations of PMRs. Data were obtained, coded, and transcribed by company physicians and other personnel, except in the case of one company, for which deaths were coded by the state health department. Expected values were derived by applying the U.S. white male 1974 five-year age- and cause-specific proportions to the total number of deaths in the study group.

This was a study with predominantly negative results, and the author suggested that the study supports the "conclusion that work in steel plants manufacturing and processing stainless steel has not resulted in a shift in the proportion of deaths due to cancer toward cancer of the lung or cancer of the kidney, whether or not there was a potential for exposure to metallic nickel." While this statement may be correct, caution must be exercised in the interpretation of these findings and in inferring the absence of an excess risk of cancer. Although the number of deaths was large, several methodologic problems exist in relation to the period of case ascertainment, the frame for identifying cases, the latency from first exposure to death, the definition of exposure, and the opening dates of the plants. These problems severely limit any conclusions that can be drawn from this study. One striking finding, however, given the large number of deaths identified, was the complete absence of nasal cancer deaths (no expected value was derived).

Among 3,323 deaths classified as "exposed," the PMR for lung cancer was 97 compared to 80 for the nonexposed. None of the PMRs for any cancer site were above unity for those exposed. The PMR for other neoplasms was statistically less than 100 (0.91). Similarly, for the 1,164 white male deaths without potential exposure to nickel, none of the PMRs for cancer sites were greater than 100, with the exception of laryngeal cancer (PMR = 114). The PMR for lung cancer, as noted above, was 80. The PMR for kidney and ureter cancer was 35, far less than the PMR for the same site among the exposed group (PMR = 98). Although almost all of the PMRs for tumor sites were less than 100 (note the PMR above for laryngeal cancer) for both the exposed and unexposed workers, the PMRs for two cancer sites of importance, cancer of the lung and cancer of the kidney and ureter, in addition to the category labeled "other neoplasms," were higher among the exposed workers than among the nonexposed workers.

There are several major problems with this study, in addition to the limitations which are characteristic of the typical PMR analysis. No information was used relating latency from first exposure and calendar time of employment to cancer. Exposure was defined in terms of metallic nickel. Two categories of exposure were defined. Nickel-exposed workers were considered to be those involved in "any operation in which nickel-bearing steel or nickel alloys are processed or handled" for any length of time. All other workers were considered unexposed. Given this definition, the exposed group probably comprised a large number of short-term workers and longer-term workers with variable degrees of exposure. As a result, any excess risk among a more homogeneously defined group with probable high exposure could have been significantly obscured.

8.1.10.7 Nickel-Cadmium Battery Workers (England). Sorahan and Waterhouse (1983) performed a cohort mortality study of 3,025 nickel-cadmium workers. While the study focused on exposure to cadmium and not nickel, battery makers were listed in the NIOSH criteria document (1977) as having potential occupational exposure to nickel, and the authors stated that, except for one high-exposure job, "all jobs entailing high cadmium exposures were also associated with high nickel exposure." The nickel exposure in this setting was primarily nickel hydroxide.

In this study, 3,025 workers (2,559 men and 466 women) who worked at least 1 month between 1923 and 1975 were followed for vital status through January 31, 1981. The authors stated that "mortality was investigated for the period 1 January 1946 to 31 January 1981." Thus it would appear that all 3,025 members of the cohort were known to be alive on December 31, 1945, which would imply that the members of the cohort who began work between 1923 and 1945 were "survivors" to the end of 1945. This is an important point, because exposure in the earlier years had been much greater than in recent times. The authors stated that "in the early factories there was little exhaust ventilation," and that measured levels of airborne cadmium were reduced dramatically "after installation of extensive exhaust ventilation in 1950," with even lower levels having been achieved in 1967. The definition of the study cohort as those workers who survived through the end of 1945 would have tended to exclude many of the workers with the greatest exposures, and would especially have tended to exclude those who were most susceptible to the effects of such exposures. This bias might have limited the power of the analysis to indicate a real relationship between high exposure levels and mortality.

Death certificates were obtained, and underlying causes of death were coded using the Eighth Revision of the ICDA. SMRs were calculated based on age-, sex-, and calendar year-specific mortality rates for England and Wales.

Overall, the SMRs showed a statistically significant excess of respiratory cancer deaths among men and women combined: 89 deaths observed, 70.2 expected, SMR = 127, $p < 0.05$. The excess was not seen among women when they were analyzed separately (SMR = 91). Among men employed between 1923 and 1946, the SMR for respiratory cancer was 123 (O/E = 52/42.4), while for men employed between 1947 and 1975, the SMR was 137 (O/E = 35/25.6) In the discussion section, the authors acknowledge that the "survivor population effect" could have produced an underestimated SMR in the early employment group.

In an analysis using regression models in life tables, workers who died were matched to all workers who survived at least until the year of death of the index case, controlling for sex, year of hire, age at hire, and duration of employment or employment status. The effects of time in high-exposure jobs and of time in high- or moderate-exposure jobs were analyzed. The results showed a significant effect of duration of employment in a high- or moderate-exposure job on respiratory system cancer deaths and prostate cancer deaths.

It was not possible to attribute the excess in respiratory system deaths to nickel or to cadmium, since the two exposures occurred at high levels simultaneously. However, because prior studies suggested an association between cadmium exposure and lung and prostate cancer deaths, and since no nasal cancer deaths (which would have implicated nickel) were seen, this study provides evidence neither for nor against a carcinogenic effect of nickel hydroxide.

8.1.10.8 Stainless Steel Welders (Sweden). The study by Sjogren (1980), which focused on exposures of stainless steel welders to chromium, is relevant here because such workers are also exposed to nickel primarily in the form of nickel oxides.

The author assembled a cohort (234 men from 8 different Swedish companies) who had welded stainless steel for at least 5 years between 1950 and 1965. Mortality was traced through December 1977, and death certificates were obtained. Expected numbers of deaths were calculated using Swedish national age- and year-specific rates, applied to person-years accumulated after the initial five years of welding experience.

While no excess of deaths of cancers of all sites was seen (4 observed versus 4.01 expected), a nonsignificant excess was observed for pulmonary tumors (3 observed versus 0.68 expected). The author concluded that the excess might have been due to inhalation of hexavalent chromium, but did not discuss the possible role of nickel.

In view of the small sample size, as well as the chromium exposure, this study is not seen as providing evidence on the question of nickel carcinogenesis.

8.1.11 Community-Based Case-Control Studies

Several community-based case-control studies have been conducted to assess the association between nickel exposure and cancer. The results from the studies are of secondary importance compared to the occupational cohort studies that have been discussed previously. The community-based studies are by definition cross-sectional, and in relation to occupational risk factors are typically insensitive. However, they can be used to estimate a calendar time-specific measure of attributable risk.

8.1.11.1 Hernberg et al. (1983). This was a case-control study of nasal and sinal nasal cancer in Denmark, Finland, and Sweden. All cases with primary malignant tumors of the nasal cavity and paranasal sinuses diagnosed in those countries between July 1, 1977 and December 31, 1980 that had been reported to the National Cancer Registers were selected for study. To ensure the quality of the data, only individuals who were alive and could be interviewed were included for study. Out of a total of 287 cases identified, 167 (110 males and 57 females) were located and interviewed. Controls with malignant tumors of the colon and rectum diagnosed over the same time period were matched to cases on the basis of country, sex, and age. Questionnaires were administered to cases and controls, and inquiries were made about occupational history, smoking history, personal habits, and hobbies. Exposure indices were developed independently of case and control status for wood dust; exposure to various metals, including chromium and nickel; and exposure to formaldehyde.

A statistically significant association was shown between the risk of nasal cancer and occupational exposure to soft wood dust alone, and more significantly to hardwood and softwood dust in combination. Twelve cases and five controls reported histories of occupational exposure to nickel. The odds ratio for nickel was 2.4, with 95 percent confidence intervals from 0.9 to 6.6. The odds ratio for chromium exposure was 2.7, which was statistically significant at the $p = 0.05$ level. In addition, those reporting exposures to chromium and/or nickel had odds ratios of 3.3, with 95 percent confidence intervals from 1.1 to 9.4.

The relative odds for exposure to nickel in this case-control study were low in comparison with some cohort studies of nickel exposure. This is in part due to the inherent limitations of a community-based case-control study for identifying occupational risk factors, and, perhaps, also due to the declining levels of exposure in work settings associated with nickel. This study provides no useful information on risks associated with a specific nickel species. The authors noted, "Chromium and nickel exposure often consisted of the welding of stainless steel, which contains up to 30 percent chromium and some nickel. These exposures mostly occur together, and can therefore not be separated statistically."

8.1.11.2 Lessard et al. (1978). This was a community-based case-control study in New Caledonia, initiated because of the strikingly high lung cancer rates on this island as compared to other South Pacific Islands. Nickel had been mined and smelted on the island since 1866. A total of 92 lung cancer cases were ascertained between 1970 and 1974, and were confirmed by reviews of medical records and pathology data. Sixty-two cases were confirmed pathologically, and 30 by means of "clinical and radiologic information." Of these cases, 81 were males and 11 were females. Controls were selected, for male cases only, from the same hospital as the cases. Subjects with neoplastic disease were excluded. The controls, which were not age-matched, had been admitted to the hospital during the summer of 1975. The method of selection was not discussed. Most of the controls were interviewed about occupational history, smoking habits, residential history, and demographic variables. Since most of the cases were deceased, information was obtained from medical charts, death certificates, administrative files, worker compensation files, and the records of the nickel company. A person was considered "not exposed" if a history of nickel exposure was not reported by any of these sources. Information on smoking habits was available for 68 of the 81 male cases. A total of 109 control subjects were included for the analysis.

The cases and controls were markedly different as to age. Fifty-one percent of the controls were less than 45 years of age, whereas only 6 percent of the cases were less than 45 years of age. In contrast, 54 percent of the cases were 55 years of age or older, and only 17 percent of the controls were above 55 years of age. Forty-three percent of the cases were classified as having a history of nickel exposure, whereas 20 percent of the controls were classified as such. Given the description of the data collection methods, it is not clear if different sources of information were used to classify cases and controls as nickel-exposed. The authors stated that "lung cancer and nickel occupation were significantly associated independently of the effects of age and cigarette smoking." The relative risk was 3.0 ($p < 0.05$). No significant interaction was noted between cigarette smoking and occupational exposure to nickel.

It is noteworthy that 66 of 68 cases and 69 of 109 controls reported histories of smoking. However, 13 of the 81 cases were excluded because there was no data on smoking history in the medical record. If smoking history among male lung cancer patients is more likely to be recorded in the medical record for smokers, then the proportion of nonsmokers among cases would be underestimated. The very high relative odds for ever smoking and lung cancer (RO = 22) suggests that proportionately more nonsmoking cases were excluded. [For ever smoked versus never smoked, one expects a RO in the range of 4.5 to 14.0 (U. S. Department of Health, Education, and Welfare, 1979)]. Although the study reported a positive association between nickel exposure and lung cancer, several factors must be considered. The method of selecting controls was not defined. Controls were selected from those admitted to the hospital after the calendar time period during which cases were identified. The cases and controls, as noted, were quite different in their distribution by age, and it is not clear that any statistical adjustment procedure would have adequately controlled for the differences on this variable. Finally, the method of ascertaining exposure information on cases and controls appears to have been different.

Langer et al. (1980) noted that the ore mined and smelted in New Caledonia was derived from serpentinized host rocks. These rocks contained large amounts of chrysotile asbestos. As a result, asbestos exposure in the mining and smelting operations must be considered when evaluating the relationship between nickel exposure and lung cancer.

8.1.11.3 Burch et al. (1981). This was a community-based case-control study of cancer of the larynx in southern Ontario. Two hundred fifty-eight cases histologically confirmed as cancers of the larynx and diagnosed between March 1977 and July 1979 were identified at two hospitals. Of the 258 cases, 204 were interviewed (184 males and 20 females). Sex- and age-matched neighborhood controls were selected. Cases and controls were interviewed about smoking history, alcohol consumption, and occupational history. Specific probes were developed for nickel and asbestos exposure, and separate measures of asbestos and nickel exposure were derived from the occupational histories.

Significant associations were found for cigarette smoking, cigar smoking, cigarillo and pipe smoking, and alcohol consumption. Fourteen cases and nine controls were identified with histories of occupational exposure to asbestos. The relative odds of exposure to nickel, adjusted for cigarette smoking, were 2.3 (p = 0.052). Thirteen cases and 11 controls were classified with histories of occupational exposure to nickel. The relative odds adjusted for smoking were 0.9, which is not statistically significant. The results of this study suggest that nickel exposure was not a risk factor for laryngeal cancer cases diagnosed between March 1977 and July 1979.

8.1.12 Summary of Epidemiologic Studies

Published and unpublished epidemiologic studies of workers in more than 16 different industrial settings have been reviewed to evaluate the epidemiologic evidence for the carcinogenic risk of nickel exposure in humans. The industries are listed in Table 8-10, with the date of the most recent publication reviewed for each. The most extensive sets of investigations were of workers at the sulfide matte refineries in Wales and Norway, and the sulfide ore mining and refining operations in Ontario, Canada. A number of reports have been issued recently on workers in the alloy metals industry, electroplating operations, and other end use activities with nickel. These investigations also are covered in this review.

Cancers of the nasal cavity and lung were the first reported tumors associated with nickel exposure. In later investigations, other sites were involved, and include cancers of the larynx, kidney, and prostate. The risks of these cancers and other nonmalignant conditions are discussed for cases in which the relevant data were included in the reports.

The evidence accumulated to date strongly suggests that nickel is a carcinogen in humans. Specifically, smelting and refining of sulfide nickel ores have been found to be associated with tumors of the lung and nasal cavity. However, it is not possible at this juncture to identify with certainty the nickel species which act as carcinogens in humans. The available information is inadequate to clearly define the process changes that have taken place at the mining, smelting, and refining operations in Canada, Wales, Norway, and the U.S., and the associated changes in exposure to nickel species and related substances. In addition, in most of the available studies, the epidemiologic data have not been analyzed to determine if changes in process corresponded to changes in risk. Hopefully, results of the nickel speciation research project, mentioned in the Introduction of this report, will help to clarify the exposures of individual workers to specific nickel compounds. Nevertheless, within the limitations of the information available, an effort has been made herein to discuss health risks in relation to selected nickel species.

TABLE 8-10. INDUSTRIES FOR WHICH EPIDEMIOLOGIC STUDIES OF CANCER RISKS FROM NICKEL (Ni) EXPOSURE HAVE BEEN REVIEWED

	Industry	Year of most recent report reviewed
I.	Ni ore mining	
	Sulfide ore	
	Falconbridge, Ontario	1984
	Sudbury, Ontario	1982
	Oxide ore	
	Hanna, Oregon	1981
	New Caledonia	1978
II.	Ni ore refining	
	Sulfide ore - Pyrometallurgical processes	
	Coniston, Ontario	1984
	Copper Cliff, Ontario	1984
	Falconbridge, Ontario	1984
	Sulfide ore - Hydrometallurgical processes	
	Fort Saskatchewan, Alberta	1984
	Oxide ore	
	Hanna, Oregon	1981
	Noumea, New Caledonia	1978
	RSFSR, Soviet Union	1973
III.	Ni matte refining	
	Clydach, Wales	1984
	Copper Cliff, Ontario	1984
	Port Colborne, Ontario	1984
	Falconbridge, Norway	1982
	Huntington, West Virginia	1982
IV.	Electrolytic refining	
	Falconbridge, Norway	1982
	Port Colborne, Ontario	1959
V.	Ni metal use	
	Die-casting and electroplating	1981
	Polishing, buffing, and plating	1980
	High Ni alloy manufacturing	1984
	Ni alloy manufacturing	1981
	Ni/chromium alloy manufacturing	1984
	Stainless steel and low Ni alloy manufacturing	1984
	Ni "barrier" manufacturing	1984
	Ni-cadmium battery manufacturing	1983
	Ni alloy welding	1981

Cohort studies have provided the most reliable estimates of these risks, and the interpretation of risks from such studies generally should supersede the results of PMR or case-control studies if there is a conflict in results. On occasion, studies of two different plants with similar methods of processing have yielded results which are in apparent contradiction. However, in such cases, a number of factors must be considered: differences in the definition of the cohort, including calendar time of exposure and age composition of the cohort; differences in definition of exposure categories, e.g., inclusion of all workers ever exposed versus exclusion of workers with limited work duration; the size of the cohort and length of follow-up, i.e., factors associated with statistical power and cancer latency from first exposure, both of which have been found to be quite variable between studies; and method of analysis and adequacy of adjustment for potential confounding variables such as calendar time, length of employment, and age. Given these limitations on the interpretation of results between studies, some conclusions have been drawn from the literature.

The disease risks by industry are summarized in Table 8-11. Some of the SMRs shown in Table 8-11 are based on subgroup analyses and were chosen for their information value in this summary section, although these SMRs may not correspond directly to risks cited in the text. In some cases, the SMRs in Table 8-11 provide a more definitive measure of risk for subgroups of workers defined by exposure to a process, by calendar time of exposure, or by length of time followed.

The risks from nickel exposure are first summarized for the mining and refining of nickel ore. Two types of nickel ore are mined and refined: sulfide nickel ore, which is the predominant form, and oxide nickel ore (International Nickel Company, Inc., 1976). The risks from each of these types of ores are discussed. Finally, risks from nickel exposure in other settings are summarized.

8.1.12.1 Mining of Nickel Ore. The sulfide ore mining operation does not appear to have been associated strongly with respiratory cancers in the study of INCO miners in the Sudbury area of Ontario (Roberts and Julian, 1982), but mining of ore from the same Sudbury area by Falconbridge workers does show a significantly increased risk of lung cancer (SMR = 142) and laryngeal cancer (SMR = 400) (Shannon et al., 1983, unpublished). Prostate cancer was significantly increased among miners in the INCO study (SMR = 167) but not in the

TABLE 8-11. SUMMARY OF CANCER RISKS BY NICKEL INDUSTRY AND WORKER GROUPS

	Cancer risks						
Industry	Lung	Nasal	Larynx	Buccal and pharyngeal	Kidney	Prostate	Other cancer/ comments
I. Ni ore mining							
Sulfide ore							
INCO, Sudbury, Ontario (Roberts and Julian, 1982)	105	166	102	--	137	167^b	15+ years since first exposure. Pancreas (142^a).
Falconbridge, Ontario (Shannon et al., 1983)	142^a	None	400^a	45	55	78	Larynx (1145^a) among men with less than 5 years of exposure and with at least 20 years since first exposure.
Oxide ore							
Hanna, Oregon (Cooper and Wong, 1981)	128	None	None	None	--	--	Sulfur-free ore.
II. Ni ore smelting and related processes							
Sulfide ore - Pyrometallurgical processes							
Falconbridge, Ontario (low temp. sintering) (Shannon et al., 1983)	131	None	196	89	None	219	Smelter workers. Lung SMR = 214 when analysis was limited to sinter workers.
Coniston smelter (low temp. sintering) (Roberts et al., 1982 and 1983)	286^a	None	None	None	None	559	Lung cancer SMR for workers with >5 years of exposure and $\geq$15 years since first exposure was 581^b.
Sulfide ore - Hydrometallurgical processes							
Fort Saskatchewan, Alberta (Egedahl and Rice, 1984)	None	None	None	1 case	303	None	Nickel workers (not maintenance) Colon & rectum (363) Lower lip (357).
Oxide ore							
Smelting Hanna, Oregon (Cooper and Wong, 1981)	72	None	393	None	--	--	Sulfur-free ore. Ever employed in smelting, refining furnaces, skull plant, or ferrosilicon area.

(continued on the following page)

TABLE 8-11. (continued)

Industry	Lung	Nasal	Larynx	Cancer risks Buccal and pharyngeal	Kidney	Prostate	Other cancer/ comments
III. Ni matte refining							
Clydach, Wales (Peto et al., 1984)	510^b	$26,667^b$	--	--	--	--	Among workers starting before 1925.
Copper Cliff, Ontario (Roberts and Julian, 1982)	424^b	1583^b	None	None	None	251 (All Sudbury)	May not include all men exposed to ore processing.
Port Colborne, Ontario (Roberts et al., 1983)	298^b	9412^b	None	299^a	213	74	
Falconbridge, Norway (Magnus, et al., 1982)	360^b	4000^b	670^b	--	--	--	
Huntington, W.Va. (Enterline and Marsh, 1982)	118	2443^b	None	--	--	--	Has received feed from both Canada and New Calendonia.
IV. Electrolytic refining							
INCO, Port Colborne (Sutherland, 1959)	105	None	--	--	--	--	Workers with "pure" exposure history.
Falconbridge, Norway (longest job held) (Magnus et al., 1982)	550^b	2670^b	None	--	--	--	
V. Ni metal use							
Die-casting and electroplating (Silverstein et al., 1981) (PMR)	195^b	None	330	77	96	--	PMRs for white males.

(continued on the following page)

TABLE 8-11. (continued)

	Cancer risks						
Industry	Lung	Nasal	Larynx	Buccal and pharyngeal	Kidney	Prostate	Other cancer/ comments
Polishing, buffing, plating union (Blair, 1980) (PMR)	106	None	143	?	111	111	Esophageal (185[a]). Primary liver (278[a]).
High Ni alloy manufacturing (Redmond, 1983)	100	None	71.2	--	--	104	20+ years employment (white males).
Ni alloy manufacturing (Cox et al., 1981)	124	None	--	--	--	--	
Ni/chromium alloy manufacturing (Landis and Cornell, 1981) (PMR)	148[a]	None	None	--	--	75	PMRs in white males who died at age 65+.
Stainless steel and low Ni alloy steel manufacturing (Cornell, 1979) (PMR)	97	None	79	--	--	98	
Ni "barrier" manufacturing (Cragle et al., 1983)	59	None	None	292	None	92	Liver (387).
Ni-cadmium battery (Ni hydroxide) (Sorahan et al., 1983)	127[a]	None	--	--	--	121	Cadmium exposure.
Ni alloy welding (Polednak, 1981)	124	None	--	--	--	--	

[a] $p < 0.05$.

[b] $p < 0.01$.

None = No cases observed.

-- = The site-specific tumor was not studied, not reported, or not specified for the defined group of workers.

PMR = Proportionate mortality ratio study.

NOTE: While this table does summarize positive evidence of increased risks, the lack of such evidence may be attributed merely to factors such as study design, cohort definition, length of follow-up, bias, or lack of statistical power, etc. Generally, the one most appropriate report for each worksite was chosen for use in this summary table. Refer to the text of this report for the critique.

Falconbridge study (SMR = 78). However, the designs of both studies created an overlap of exposure classification among mining and other processes, which may have spuriously increased or decreased the miners' actual cancer risks. The possibility also exists that the cancers among miners may not have resulted from nickel exposures at all but from exposures to other potential carcinogens encountered in the mines, although Roberts and Julian (1982) did state that the Ontario ore contained no asbestos-like material and that radon daughters were low in the Sudbury mines. However, a worker was defined as a miner in the Falconbridge study if he "ever worked" in the mines. As a result, there is the possibility that an individual classified as a miner could have been employed for sometime in the smelting or refining operation.

Cohort studies reviewed of risks associated with oxide nickel ore include a study of workers at the Hanna mining and refining plant in Oregon (Cooper and Wong, 1981). No excess risk of lung or nasal cancer appears to have been associated with oxide nickel ore mining. The follow-up period for the cohort was relatively short compared to studies of other miners, especially since the latency periods for nasal and lung cancers are long. While there was a maximum of 24 years of follow-up from first exposure, only 1,192 person-years of observation were accumulated in workers with more than 20 years after first exposure.

8.1.12.2 Nickel Ore Smelting and Related Processes. Sulfide nickel ore is processed at INCO's Copper Cliff and Coniston facilities, and at Falconbridge, Ltd.'s Falconbridge, Ontario plant. Analyses of cancer risks associated with the early stages of processing of sulfide nickel ore showed no excess risks among workers at Copper Cliff in smelting and converting of sulfide nickel ore (Sutherland, 1971). However, these data were not analyzed in such a way that cancer risks among those employed before and after process changes can be separated. At the Coniston and Falconbridge smelters, only small increases in lung cancer risks were seen (statistically significant at Coniston but not at Falconbridge). Coniston sintering workers experienced a nonsignificant increase in prostate cancer deaths (SMR = 559), while Falconbridge workers had a nonsignificant excess of laryngeal cancer (SMR = 196). Since the ores for both plants were obtained from the Sudbury, Ontario nickel deposit, and the low-temperature sintering process is said to have been the same at both places, any differences in exposure that could account for the slight differences in risks are likely to be subtle.

No excess risk of lung or nasal cancer appears to have been associated with refining of sulfur-free, oxide nickel ore. Laryngeal cancer was found to be in excess among all workers at the Hanna, Oregon plant, but the SMR was not statistically significant. A statistically significant SMR was found, however, for laryngeal cancer among employees who were still working 15 or more years after beginning employment (SMR = 909, $p < 0.05$). The follow-up period for the cohort was relatively short compared to studies of other refinery workers, especially since the latency periods for respiratory cancers are long. While there was a maximum of 24 years of follow-up from first exposure, only 1,192 person-years of follow-up were accumulated more than 20 years after first exposure. Moreover, the exposure levels at Hanna may have been considerably lower than the levels encountered at sulfide nickel ore sites such as Sudbury, Ontario, which may result in a lower relative risk and longer latency than experienced at the other refineries.

8.1.12.3 Nickel Matte Refining. In the early years of the refineries, INCO's Sudbury area facilities were producing crude converter matte, some of which was sent to other facilities for further refining while some was refined at Copper Cliff. This matte was further refined using either the carbonyl process (Clydach and Copper Cliff) or electrolysis (Port Colborne). The composition of this converter matte was changed in approximately 1948, which resulted in a lower copper and sulfur content than was present in the matte prior to 1948. By 1963, and possibly earlier, Copper Cliff was supplying the other sites with a matte that had already been oxidized to nickel oxide.

In the case of the Clydach refinery, several changes were made in the material used as feed to the plant. From 1902 to 1932, the refinery had received converter matte directly from Copper Cliff, Ontario, and separation by the Orford process was done on-site in Wales. From 1932 to 1948, Clydach received low-copper nickel matte and discontinued its Orford process. Throughout its operation, the carbonyl process was used in the final step of refinement.

Before 1930 at Clydach, Wales, the predominant nickel species from the refining of nickel matte were nickel subsulfide, nickel sulfide, nickel oxide, and nickel carbonyl. Other exposures included copper sulfate, arsenic, and trace elements of selenium and cobalt. There was an extraordinarily high risk of lung and nasal cancer among Clydach workers who started their employment before 1925. The SMR for nasal cancer was highest for workers starting between

1910 and 1914 (SMR = 64,900). The risk began to decline after 1914 (SMR = 9,900 for those first employed between 1920 and 1924), and no cases of nasal cancer occurred among workers first employed after 1924. Gauze masks were introduced in the plant between 1922 and 1923, and were found to be correlated with a virtual absence of nasal cancer after 1924. Studies by INCO (1976) showed that the gauze mask effectively reduced the total dust exposure (60 to 81 percent efficacy with one pad and 85 to 95 percent efficacy with two pads) and altered the size distribution of dust particles. The fact that the risk of nasal cancer began to decline after the introduction of masks may, in part, have been an artifact of the cohort definition, i.e., workers starting earlier who met the cohort criteria by definition had to have worked longer.

The other notable change in the process at Clydach was in the calcining step. However, the data do not permit determinations as to when the changes took place, or their effects on exposures. The risk of lung cancer, in contrast to nasal cancer, was high among workers starting employment before 1920, and peaked among workers starting between 1920 and 1924 (Peto et al., 1984). Doll et al. (1977) showed that the lung cancer risk was still in excess and appeared to be increasing with continued follow-up for workers starting between 1925 and 1929. Peto et al. (1984) noted that the highest risks of lung and nasal cancer were associated with the copper sulfate process and the Orford furnace. However, very high risks for both of these tumors appear to have been associated with other aspects of the refining process as well, since those who did not work in either the furnace or copper sulfate area had an excess risk of lung (SMR = 340) and nasal (SMR = 14,700) cancers.

Cancer risks in matte refining at Copper Cliff were found to be very high for nasal cancer (SMR = 1583, $p < 0.01$) and significantly high for lung cancer (SMR = 424, $p < 0.01$) among men with any exposure to sintering (Roberts et al., 1982). The process implicated treats a low-copper feed with downdraft traveling grate sintering machines at high temperatures (1,650°C); exposures may have included nickel sulfide, subsulfide, and oxide, as well as coke particles and polycyclic aromatic hydrocarbons (International Nickel Company, Inc., 1976).

At Port Colborne from the 1920s to 1973, nickel copper matte from Copper Cliff was calcined in enclosed calciners to oxidize nickel subsulfide. From 1926 to 1958, sintering at high temperatures was used after calcining to oxidize the ignited sulfur charge, using traveling grate sinter machines on an open hearth at 1,650°C, with the addition of coke. According to Roberts et al.

(1982), the calcining/sintering process was dusty, and caused exposures similar to those in the calcining sheds at Clydach.

At Port Colborne, Sutherland (1959) showed high risks of both lung and nasal cancers (SMR = 379 and 2,874, respectively) among men whose entire work histories were spent as furnace workers (cupola, calciners, sinter, and anode furnace). These workers included men who had been exposed before and after the changes in the feed from high to low copper concentration and to nickel oxide. The author did not present sufficient data to enable the separation of exposures. Based on mortality follow-up of a somewhat differently defined cohort, Roberts et al. (1982) continued to find high risks among men "ever exposed" to leaching, calcining, and sintering. Among workers with at least 15 years since first exposure, the SMR for lung cancer was 298; the SMR was 445 ($p < 0.01$) in the subgroup with at least 5 years of exposure. The excess risk of nasal cancer was shown by a very high SMR of 9,412, which is consistent with the findings at other matte refineries. However, it is not clear that all of the excess risk can be attributed to sintering, since a large proportion of all of the lung and nasal cancer cases had worked for short periods in the sintering department and for long periods in other departments, including electrolysis (International Nickel Company, Inc., 1976).

At the Falconbridge refinery in Norway, the highest risk of nasal cancer was found in roasting and smelting (R/S) workers, who were exposed primarily to particulate matter containing nickel subsulfide and oxide. This association was strengthened by the fact that R/S workers had the highest nasal mucosal nickel levels, and had the most frequent and severe mucosal dysplasia among the current workers. The highest risk of lung cancer was found in electrolytic workers who had been exposed primarily to aerosols of nickel sulfate and chloride. Although the ambient levels of nickel were higher in the electrolytic tankhouse, the nasal mucosal levels of nickel for these workers were the lowest of all process workers. In contrast, the urine and plasma levels were highest in these workers.

There appears to have been an association between the occurrence of laryngeal cancer and the disappearance of nasal cancer at the Falconbridge refinery in Norway. Four of 5 laryngeal cancer cases were first employed on or after 1940, whereas only 1 of 14 nasal cancer cases occurred among those starting after 1940. The refinery appears to have been inactive between 1940 and 1945, with changes in production and control measures being introduced after

1945. It would be of interest to know the relationship of such control measures with changes in dust levels and particle size distribution, and the specific nickel species involved. As an alternative explanation, the increased risk of laryngeal cancer could reflect changes in smoking patterns. However, data were not presented to address this question directly.

The oxidation process in the final refining of the impure nickel sulfide has varied between calcining and sintering at the different sites in different time periods. The fuels in these steps, and the temperatures needed for the processes, have also varied. Some plants have used an electrolytic separation method, while others have used a carbonyl process. All of these changes, as well as control measures, could have resulted in differences in exposures over time at these facilities.

In summary, sulfide ore smelting and refining have been found to be associated with excess risks of lung, nasal, and laryngeal cancers, and possibly buccal and pharyngeal, prostate, and kidney cancers. A clear delineation of these risks is problematic, however, because of the complex operational changes at the INCO Sudbury (Ontario), Port Colborne, Coniston, and Clydach (Wales) facilities, all of which are related to each other and to those in Huntington, W. Va., through the use and exchange of common products. Because of the inadequacy or inconsistency of the available information, it is not possible to state with certainty how changes in the operation at one facility affected the materials processed at another facility, or to relate these changes to changes in exposure and in risk. In addition, exposure was typically defined on the basis of longest job held. As a result, the risks associated with a specific processing step may, in part, be accounted for by employment in other areas of a plant.

In conclusion, several general patterns are noteworthy. The risk of lung and nasal cancer among miners has been found to be low in comparison with the risks among smelter and refinery workers, although there does appear to have been some excess risk for lung, nasal, and laryngeal cancers at the Sudbury and Falconbridge mines. Sulfide ore processing at Falconbridge (Ontario) and Coniston was not associated with an excess risk of nasal cancer, but was associated with an excess risk of lung cancer. However, the lung cancer risk was found to be low in relation to that among nickel matte refinery workers. The risk of nasal cancer was shown to be exclusive to sulfide nickel matte refinery workers, and appears to have been restricted primarily to smelter workers. The electrolytic tankhouse workers at Falconbridge, Norway, showed a large excess risk of nasal cancer (Magnus et al., 1982) while tankhouse exposure at Port Colborne was not associated with lung cancer (International Nickel Company, Inc., 1976, unpublished).

8.1.12.4 Other Nickel-Related Industries. Nickel exposures may occur in several other industries and at other worksites. The form of the nickel varies, and can include metal alloys, powders, and salts. The exposures may occur in the manufacture of the nickel-containing products, such as in stainless steel or nickel-cadmium batteries, or may occur in end-uses of nickel, such as in electroplating or welding. Worker populations in several of these industries were examined, but in most cases the risks were not found to be high. On the other hand, the studies generally were not rigorous or did not attempt to separate the risks associated with nickel from the risks associated with other metals or materials in the environment. It is important that advantage be taken of appropriate opportunities to obtain more information on exposures to nickel in species and situations not related to refineries.

8.2 EXPERIMENTAL STUDIES

Experimental carcinogenesis has been the subject of numerous reviews (Sunderman, 1984a,b,c, 1983, 1981, 1979, 1977, 1976, 1973; Rigaut 1983; National Institute of Occupational Safety and Health, 1977a; International Agency for Research on Cancer, 1976; National Academy of Sciences, 1975). The qualitative and quantitative character of the carcinogenic effects of nickel, as seen in experimental studies, has been shown to vary with the chemical form and physical state of nickel, the route of administration, the animal species and strain employed, and the amounts of nickel compound administered.

The following sections will discuss animal studies by inhalation and ingestion, as these are most relevant to the assessment of potential human risk from environmental exposures to nickel. The carcinogenesis testing data for specific nickel compounds, as well as relevant chemical and biological indicators, will then be summarized to promote an understanding of our current knowledge of the carcinogenic activities of these compounds.

8.2.1 Animal Studies by Inhalation and Ingestion

8.2.1.1 Inhalation Studies. Ottolenghi et al. (1974) exposed Fischer 344 rats to an airborne nickel subsulfide (Ni_3S_2) concentration of 0.97 mg nickel/m^3 (70

TABLE 8-12. 2^4 FACTORIAL DESIGN OF NICKEL SUBSULFIDE RAT INHALATION STUDY OF TWO PREEXPOSURE SUBTREATMENTS FOLLOWED BY 78-WEEK EXPOSURE[a] (16 SUBGROUPS)

	Subtreatment							
	Preexposure				No Preexposure			
	Injection		No Injection		Injection		No Injection	
Treatment	M	F	M	F	M	F	M	F
Control	29	28	28	30	32	32	31	31
Ni_3S_2	29	28	22	26	39	24	32	26

[a] Preexposure subtreatment for one month to Ni_3S_2 followed by subtreatment of intravenous injection with hexachlorotetrafluorobutane.

Source: Ottolenghi et al. (1974).

percent particles smaller than 1 μm) 6 hours/day, 5 days/week, for 78 to 80 weeks. The animals were observed for an additional 30 weeks thereafter. The design of the study, matrixed in Table 8-12, included two subtreatments in a 2^4 factorial arrangement: a total of 467 rats of both sexes (factor 1) were used in the design which incorporated a preexposure subtreatment for one month to nickel subsulfide (0.97 mg Ni/m^3, 6 hrs/d, 5 d/wk), followed by the second subtreatment of intravenous injection with hexachlorotetrafluorobutane (HTFB), an agent used to induce pulmonary infarction. The fourth factor was the actual treatment (after the injection factor) with nickel subsulfide for 78 to 80 weeks. Following the exposure period, the animals were observed for an additional 30 weeks before terminal sacrifice.

The design of the 2^4 arrangement, resulting in the 16 subgroups (Table 8-12), allowed simultaneous estimation of the effect of each of the four factors (sex, pretreatment, HTFB injection, Ni_3S_2 treatment) in a combined analysis using an additive effects model. This analysis appears to have been done only partially, using a Mantel-Haenzel procedure. Some of the reported results are noted below.

(1) With respect to mortality, there was no difference between males and females or between the injection versus the no injection subgroups; preexposure to nickel subsulfide caused a slight increase in early deaths among male rats. For the nickel subsulfide treatment group, the results were clear-cut; all eight nickel subsulfide groups showed a higher mortality when compared with their corresponding control groups. This difference first appeared during the 52-

to 78-week exposure period ($p < 0.05$ for males; $p < 0.10$ for females), and was accentuated ($p < 0.01$) during the final 30 weeks before sacrifice. Combining sexes and pretreatment groups, fewer than 5 percent of the nickel subsulfide-treated rats were alive at the end of 108 weeks, as compared with 31 percent of the controls.

(2) Body weight changes were reported to be similar to mortality effects, with all eight nickel subsulfide-treated subgroups showing a time-related reduction versus the corresponding control groups. None of the pretreatments had a consistent effect.

(3) The lungs were most affected by nickel subsulfide treatment, but no differences in response were attributed either to sex differences or to the injections of HTFB. Of the rats receiving HTFB, 15 percent had lung tumors compared with 13 percent of the untreated animals. Also, the injections of HTFB produced lung infarctions in 32 percent (35 of 109) of the controls, compared with only 14 percent of the nickel subsulfide-treated rats (35 of 109), so that there appears to be no synergistic effects of HTFB and nickel subsulfide on lung tumors.

The major lung effects of nickel subsulfide are presented in Table 8-13, combining the subtreatment groups taken from the Ottolenghi et al. (1974) paper. Here it is seen that nickel subsulfide treatment causes hyperplasia, metaplasia, adenomas, and adenocarcinomas equally in both males and females. Furthermore, these changes and tumors were in both the bronchiolar and alveolar regions.

Historically, the first attempts to confirm the carcinogenic potential of airborne nickel are the studies of Hueper (1958) and Hueper and Payne (1962). Hueper (1958) reported a study of the carcinogenic potential of airborne concentrations of elemental nickel. The experimental animals were exposed to 99 percent pure nickel, 4 μm or less in size, at a concentration averaging 15 mg/m^3 for 6 hours/day, 4 or 5 days/week, for 24 months or until death. It is not clear if the chamber concentrations were measured or calculated. Guinea pigs (32 males, 10 females), Wistar rats (50 males, 50 females), Bethesda black rats (60 females), and C57 black mice (20 females) were exposed to elemental nickel in the form of dust. By the end of the first year, 45 percent of the guinea pigs, 64 percent of the Wistar rats, 52 percent of the Bethesda rats, and 85 percent of the mice had died. All of the treated animals died by the end of the second year. The description of the study does not indicate the consistency with which organs other than the lungs were examined histopathologically. The author indicated that the mice had hyperemic to hemorrhagic

TABLE 8-13. HYPERPLASTIC AND NEOPLASTIC CHANGES IN LUNGS OF RATS EXPOSED TO NICKEL SUBSULFIDE[a]

Pathologic changes	Controls		Nickel subsulfide	
	Males (108^b)	Females (107^b)	Males (110^b)	Females (98^b)
Typical hyperplasia	26 (24)	20 (19)	68 (62)^c	65 (66)^c
Atypical hyperplasia	17 (16)	11 (10)	58 (53)^c	48 (49)^c
Squamous metaplasia	6 (6)	4 (4)	20 (18)^d	18 (18)^d
Tumors:				
Adenoma	0 (0)	1 (1)	8 (7)^e	7 (7)^d
Adenocarcinoma	1 (1)	0 (0)	6 (5)^d	4 (4)^e
Squamous cell carcinoma	0 (0)	0 (0)	2 (2)	1 (1)
Fibrosarcoma	0 (0)	0 (0)	1 (1)	0 (0)

[a] Values represent the number of affected animals in each group. Percent of affected animals is given in parentheses. Subtreatment groups were combined, as no significant differences were found among them.

[b] Number of animals.

[c] $p < 10^{-5}$, Fisher's Exact Test.

[d] $p < 0.01$, Fisher's Exact Test.

[e] $p < 0.05$, Fisher's Exact Test.

Source: Ottolenghi et al. (1974).

conditions in the pulmonary tract but showed no neoplastic reactions which were judged to be from nickel exposure. The only tumors reported among the mice were two lymphosarcomas. Thirty-seven guinea pigs were evaluated histopathologically. Seven of 8 guinea pigs dying in the first 6 months of the study had lower grades (1 and 2) of adenomatoid proliferations, while 20 of 29 pigs surviving 7 to 21 months had higher grades (3 and 4). In six animals, the author reported that the intra-alveolar and intrabronchiolar epithelial proliferations approached "the character of microcarcinomas." In addition, one guinea pig had an intra-alveolar carcinoma, while a second was found to have a retroperitoneal node judged to originate from a pulmonary carcinoma. Fifteen of 50 rats evaluated histopathologically had adenomatoid formations. The author concluded that lung lesions in the rats and guinea pigs were "equivalents of the respiratory neoplastic reactions seen in copper-nickel matte smelter workers." Although suggestive lesions were found in rats and guinea pigs, the data presented do not clearly indicate carcinogenicity attributable to elemental nickel. Because of the poor survival times of the animals in this study (less than two years), the data contained in the study report cannot be considered adequate for the assessment of carcinogenicity.

Hueper and Payne (1962), experimenting with rats and hamsters, attempted to confirm the carcinogenic potential of nickel previously reported. Airborne powdered nickel, particle size 1 to 3 μm, was administered with sulfur dioxide and powdered limestone. (The limestone was added to prevent the nickel particles from forming conglomerates, to dilute the nickel, and to decrease the toxicity observed in the previous study. Sulfur dioxide was added to test its potential as a cocarcinogen.) Chamber concentrations of nickel were not specified; the animals were exposed for 6 hours/day to a mineral mixture (3 or 4 parts nickel to 1 part limestone for the hamsters, and 1 part nickel to 1 part limestone for the rats) released into the chamber at 50 to 65 g/day, along with sulfur dioxide at a concentration of 20 to 35 ppm. One hundred male hamsters and 120 rats (60 males, 60 females) were exposed. All died within 24 months. Control animals were not mentioned. Cancers of the lung were not observed in the rats or the hamsters. The lungs from hamsters showed minimal effects attributable to exposure. The hamsters probably had lower exposure to nickel particulates, but in view of a likely high pulmonary burden of dust and irritant vapor, this study may only suggest that hamsters are not responsive to inhaled irritants. While the authors indicated that many of the rats had inflammatory fibrosing changes with bronchiectasis, squamous cell metaplasia, and peribronchial adenomatosis, they did not consider these changes to be malignant or premalignant as in the previous study.

Wehner and co-workers (1984) summarized their work on the toxicity and potential carcinogenicity of airborne concentrations of nickel oxide in hamsters (Wehner et al., 1975, 1981). In the 1975 study, 51 male Syrian golden hamsters (random bred ENG:ELA) were exposed to airborne concentrations of nickel oxide dust (count median diameter 0.3 µm) at a concentration of 53.2 mg/m^3 for 7 hours/day, 5 days/week for up to 2 years. A similar group was exposed (nose only) to cigarette smoke and nickel oxide for ten minutes, three times a day. A control group was maintained for each of these treatment regimens.

The histopathologic evaluation revealed that among the hamsters dying late in the study, there was an increasing cellular response of both an inflammatory and proliferative nature. There was no marked difference between the nickel-oxide-plus-smoke and the nickel-oxide-only treatment effects, except for brownish cytoplasmic inclusions and an increase in laryngeal lesions in the former group. The authors concluded that while lung lesions (massive pneumoconiosis) developed from chronic exposure to nickel oxide, "neither a significant carcinogenic effect of the nickel oxide nor a cocarcinogenic effect of cigarette smoke" was found. However, it is noteworthy that three malignant musculoskeletal tumors (two osteosarcomas and a rhabdomyosarcoma in the thoracic skeletal muscle) were found among the nickel oxide-exposed hamsters. No such tumors were present among the control animals. A rhabdomyosarcoma is the same type of tumor produced by injection of nickel oxide.

Wehner et al. (1981) also investigated the effects of chronic inhalation of nickel-enriched fly ash (NEFA) in the Syrian golden hamster (outbred LAK:LVG). Four groups of 102 male hamsters were exposed 6 hours/day, 5 days/week, for up to 20 months. The first group was exposed to 70 µg/l of NEFA which contained approximately 6 percent nickel. The airborne concentrations were reported as "respirable aerosol concentrations" based on measurement with a cascade impactor. No further details were given. The second group was exposed to 17 µg/l of NEFA (6 percent nickel). The third group was exposed to 70 µg/l of fly ash (FA) which contained 0.3 percent nickel, while the fourth group was exposed to filtered air and served as a control group. Five animals from each group were killed after 4, 8, 12, and 16 months of exposure. In addition, five animals were withdrawn from exposure at the same time intervals and maintained without exposure until the end of the study, when all surviving animals were killed. The mean survival times were 474, 495, 513, and 511 days for the NEFA-high, NEFA-low, FA, and control groups, respectively. The lung weights and lung/body weight ratios were increased in the NEFA groups ($p < 0.01$) as compared to the controls. This trend was evident even after four months. The mean nickel lung concentrations after 20 months of exposure were 731, 91, 42, and 6 μg, respectively. The authors suggested that the apparent increased retention of nickel in the high-exposure group may have been due to reduced pulmonary clearance. The severity of the interstitial reaction and bronchiolization was greatest in the NEFA-high and FA-exposed groups as compared to the NEFA-low group, suggesting that these effects are related more to the actual dust concentrations than to the nickel levels. While malignant pulmonary tumors (one mesothelioma and one adenocarcinoma) were found in two hamsters of the NEFA-high group, no statistically significant carcinogenic response was evident.

The particle size in the Wehner et al. (1975) study was small compared to that in the Ottolenghi et al. (1974) study. Because of this, clearance was probably faster. The adequacy of the studies by Wehner et al. (1981, 1975) for determining carcinogenic potential is questionable, however, because of the possible lack of sensitivity of the hamsters as experimental animals to carcinogenic materials. Hueper and Payne (1962) observed a lack of pathological response of hamsters to airborne nickel as compared to rats. Similarly, Furst and Schlauder (1971) reported that rats are much more sensitive to tumor induction by nickel injection than hamsters.

Kim et al. (1976), in an unpublished inhalation study at the University of Toronto, exposed male Wistar rats to various combinations of nickel and iron dusts. There were 77, 76, and 67 rats in treatment groups I, II, and III, respectively, and one control group of 67 animals. Approximately one-half of the rats in each group were young and one-half were old. Group I was exposed to nickel powder at a concentration of 87.3 $\mu g/ft^3$ (3.1 mg/m^3). Group II was exposed to a mixture of equal weights of nickel powder, "Dust C" (24.1 percent nickel sulfate, 68.7 percent nickel sulfide, and 7.2 percent nickel oxide), hematite, and pyrrhotite. The total nickel concentration was 59.5 $\mu g/ft^3$ (2.1 mg/m^3), and the iron concentration averaged 53.2 $\mu g/ft^3$ (1.9 mg/m^3). The actual airborne concentration of nickel was not reported. Group III was exposed to an iron mixture (iron, hematite, and pyrrhotite) at an iron concentration of 85.0 $\mu g/ft^3$ (3.0 mg/m^3). Within each group, subgroups were exposed from 7 to 16 months, and identical exposure schedules were used for all three dust combinations. Ninety-eight percent of the particles were smaller than 2 µm. The rats in groups I and II (with nickel exposure) had a greater granulomatous response as compared to the controls or to the rats exposed to iron. In group I, 3 of 60 rats evaluated histopathologically had lung tumors (2 carcinomas and 1 lymphosarcoma). This group had the greatest nickel exposure. Among the 61 rats evaluated histopathologically from group II, there was only 1 lung tumor, a squamous cell carcinoma. The group III rats, exposed to an iron mixture, developed 2 carcinomas and 1 papillary adenocarcinoma among the 58 evaluated histopathologically. Among the 55 control rats evaluated histopathologically there was only 1 lung carcinoma. The authors concluded that under the conditions of the experiment, there was no evidence of lung cancer as the result of a direct carcinogenic action of the inhaled dust. The data presented in the Kim et al. (1976) report did not allow for further analysis related to latency period or to the relative effects of nickel on rats of different age groups.

Horie et al. (1985) presented limited information on the results of exposing male Wistar rats to airborne nickel concentrations. The rats were exposed 6 hours per day, 5 days per week, for 1 month to nickel oxide concentrations of 8.0 and 0.6 mg/m^3. The experimental rats of interest with regard to carcinogenic assessment were observed 20 months. There was one adenocarcinoma in the low-exposure group of the six animals examined. There were no cancers among the four rats exposed to the higher dose or among the five control animals. Because the number of experimental animals was small, this study is only qualitatively suggestive.

Sunderman et al. (1959) and Sunderman and Donnelly (1965) reported carcinogenic responses in rats variably exposed to nickel carbonyl [$Ni(CO)_4$] by inhalation. Sunderman et al. (1959) exposed 3 groups of male Wistar rats to nickel carbonyl: 64 rats were exposed to 0.03 mg/l 3 times weekly for one year; 32 rats were exposed to 0.06 mg/l 3 times weekly for 1 year; and 80 animals were exposed once to 0.25 mg/l. In each case, exposure was for 30-minute periods. Forty-one control animals were exposed to a vapor of 50 percent ethanol/ether, the solvent for the nickel carbonyl. Of the nine animals exposed to nickel carbonyl and surviving two years or more, four were reported to have tumors: one animal from repeated nickel carbonyl exposure of 0.03 mg/l, one from inhaling 0.06 mg/l repeatedly, and two from a single heavy exposure. No assessment of tumorigenicity was done on the animals that died. It is possible that tumor incidence may have been enhanced among these animals, but it is difficult to be more specific. The similar death rate for controls and treated animals suggests that no enhanced mortality due to exposure occurred. The survival rate in this study, even for controls, was lower than expected. Two of the animals showed masses of clear-cell carcinoma having an adenocarcinomatous pattern (one from the large-single-dose group and one from the group chronically exposed to nickel carbonyl at 0.06 mg/l), while one rat showed a squamous cell carcinoma (chronic exposure to nickel carbonyl at 0.03 mg/l). The fourth animal showed two small papillary bronchial adenomas (single-large-exposure group). No pulmonary tumors were seen in the three surviving controls.

In the report of Sunderman and Donnelly (1965), six groups of male Wistar rats were used. Three of these groups were control groups. Two of the control groups, 19 animals in each, were exposed to the solvent for the nickel carbonyl (ethanol/ether, 1:1) for 30 minutes in a single exposure and were either treated or untreated with "dithiocarb" nickel chelating agent. The third control group of 32 animals inhaled solvent for 30 minutes, 3 times a week, for their lifetimes. The exposure groups consisted of (a) 285 animals exposed once to 0.6 mg/l of carbonyl for 30 minutes and followed for their lifetimes, (b) 60 rats exposed as in (a) above, but receiving an injection of "dithiocarb" nickel chelate 15 minutes after exposure, and (c) 64 animals exposed for 30 minutes 3 times weekly to 0.03 mg/l carbonyl for the remainder of their lifetimes.

In the chronic and acute nickel carbonyl exposure groups, 3 animals of the 80 surviving the 2-year exposure and/or observation period showed pulmonary carcinomas with metastases, 1 with papillary adenocarcinoma, 1 with anaplastic carcinoma, and 1 with adenocarcinoma. No pulmonary neoplasms were noted in any of the 44 animals remaining in the control groups.

The two studies cited above, taken in the aggregate, reveal that 6 animals of 89 (surviving to 2 years of age or more) exposed to nickel carbonyl developed malignant lung tumors with either acute high inhalation exposure (3 animals) or chronic time-graded exposure (2 animals, exposed for 1 year; 1 animal, exposed for 26 months). It should also be emphasized that in the second study all lung malignancies had metastasized to other organs. While statistical analysis was not carried out, given the small sample size of survivors, it should be noted that spontaneous pulmonary malignant neoplasms in Wistar rats are very rare, so that even a small incidence of pulmonary malignant tumors should be of some significance.

8.2.1.2 Oral Studies. Three studies of the carcinogenic potential of nickel salts in drinking water were found in the literature (Schroeder and Mitchener, 1975; Schroeder et al., 1974, 1964). All three studies produced negative results, and all three used the same relatively low dose level of 5 ppm of nickel in the drinking water.

In the first study, Schroeder et al. (1964) gave 74 Swiss mice 5 ppm nickel acetate in drinking water for the duration of their lives. Tumors (types not specified) were reported in 10 of the 74 test animals and 33 of 104 controls. However, the diet in this study was considered to be chromium-deficient, and the study was repeated by Schroeder and Mitchener (1975). In that study, 108 male and female Swiss mice were given 5 ppm nickel acetate in their drinking water for the duration of their lives. Tumors were found in 14 of 81 test animals and in 19 of 88 controls. In the third study, Schroeder et al. (1974) exposed Long-Evans rats (52 of each sex) to drinking water containing 5 ppm of nickel (unspecified salt) for their lifetimes. The average daily nickel consumption was estimated to be 2.6 μg/rat for the controls and 37.6 μg/rat for the test animals. Similar tumor incidences were reported for the test and control groups. A slight increase (13.3 percent) of focal myocardial fibrosis was reported for the test animals as compared with controls. In these studies only one exposure level was investigated, and there is no evidence that a maximum tolerated dose was used. In addition, data on site-specific tumor incidence are not included. Therefore, these studies may be regarded as inconclusive with respect to the carcinogenic potential of 5 ppm soluble nickel in the drinking water of rats and mice.

Chronic studies of nickel in the diet of experimental animals have also been reported. The studies were conducted using much higher concentrations than those used in the rodent drinking water studies previously described, but failed to indicate any potential for the induction of cancer by nickel. Ambrose et al. (1976) administered nickel, as sulfate hexahydrate fines ($NiSO_4 \cdot 6H_2O$; 22.3 percent nickel), in the diet of Wistar-derived rats and beagle dogs for two years. The dietary nickel concentrations were 100, 1000, and 2500 ppm. There were 25 rats and 3 dogs of each sex assigned to each dose group. A similar number of untreated animals were maintained and served as controls.

The changes among the rats were minimal at the higher dietary concentrations and consisted of depressed growth rate. The females of the 1000-ppm and the 2000-ppm treatment groups showed increased heart/body weight and decreased liver/body weight ratios. The rats in the 100-ppm group had no treatment-related changes. In the dogs, only the highest level-treatment group was affected. The 2500-ppm diet depressed growth, lowered hematocrit and hemoglobin values, and increased kidney/body weight and liver/body weight ratios. Two of the six dogs showed marked polyuria. There were no other signs of toxicity reported. Histopathologic evaluation indicated no treatment-induced lesions among the rats. Among the dogs, histopathologic evaluation indicated that all dogs in the high-dose group had lung lesions, and two of the six had granulocytic hyperplasia of the bone marrow. The other treatments were without effect. The dog study may be inadequate, as the duration of the study was relatively short. The rat study would appear to be adequate to detect the cancer induction potential of the treatment and supports the lack of carcinogenic response observed in the studies of Schroeder and co-workers.

8.2.2 Animal Studies of Specific Nickel Compounds

8.2.2.1 Nickel Subsulfide. Though nickel subsulfide (Ni_3S_2) is the most studied nickel compound, only one study employed inhalation as the route of exposure. As reviewed in the previous section, nickel subsulfide predominantly produced adenomas and adenocarcinomas of the lung in Fischer 344 rats (Ottolenghi et al., 1974). Yarita and Nettesheim (1978), using nickel subsulfide pellets implanted into heterotopic tracheas grafted in Fischer 344 rats, produced mainly sarcomas with a low yield of carcinomas. Kasprzak et al. (1973) reported no pulmonary tumors in Wistar rats given 5 mg nickel subsulfide intratracheally. However, when nickel subsulfide (5 mg) was administered with benzpyrene (2 mg), the yield of bronchial metaplasia increased from 31 to 62 percent. Numerous injection studies have shown nickel subsulfide to be a potent carcinogen by injection. All routes of administration employed, with the exception of buccal brushing of Syrian golden hamsters, submaxillary implantation into Fischer rats (Sunderman et al., 1978) and intrahepatic injection of Sprague-Dawley rats (Jasmin and Solymoss, 1978) and Fischer rats (Sunderman et al., 1978), have led to positive tumor response. Table 8-14 summarizes some of the many studies on nickel subsulfide. These data are more comprehensively reviewed by Sunderman (1984b,c, 1983, 1981, 1976) and the International

TABLE 8-14. EXPERIMENTAL STUDIES OF NICKEL SUBSULFIDE CARCINOGENESIS

Nickel Compound	Animal	Route, Dose	Response	Reference
Ni_3S_2	Rat, mouse	Intramuscular, 20 mg/thigh	Rhabdomyosarcomas	Gilman, 1962
Ni_3S_2	Rats Fischer	Intrasplenic implant, 10 mg	Sarcomas in 20% of rats	Gilman, 1966
Ni_3S_2	Cats	Sinus implant (dose not given)	Epidermoid carcinomas and adenocarcinomas of sinuses	Gilman, 1970 as reviewed by Rigaut, 1983
Ni_3S_2/ benzpyrene	Rats	Intramuscular, 10 mg/5 mg	Sarcomas	Maenza et al., 1971
Ni_3S_2/ benzpyrene	Rats	Intratracheal, 5 mg Ni_3S_2/2 mg benzpyrene	Squamous cell carcinomas	Kasprzak et al., 1973
Ni_3S_2 (70% particles < 1 μm)	Rats Fischer	Inhalation, 0.97 mg Ni/m^3 6 hrs/day, 5 days/wk for 78 to 84 weeks	Adenomas, adenocarcinomas, squamous cell carcinomas in ~ 14% of treated rats	Ottolenghi et al., 1974
Ni_3S_2	Rats	Intrarenal, 5 mg/saline or glycerol	Renal adenocarcinomas	Jasmin and Riopelle, 1976
Ni_3S_2	Rats	Intratesticular, 0.6-10 mg	Fibrosarcomas and rhabdomyosarcomas	Damjanov et al., 1978
Ni_3S_2	Rats Sprague-Dawley	Intrahepatic, 10 mg	No tumors	Jasmin and Solymoss, 1978
Ni_3S_2	Rats Fischer	Intrahepatic, 5 mg	No tumors	Sunderman et al., 1978
Ni_3S_2	Rats Fischer	Submaxillary injection, 2.5 mg	No tumors	Sunderman et al., 1978

(continued on following page)

TABLE 8-14. (continued)

Nickel Compound	Animal	Route, Dose	Response	Reference
Ni_3S_2	Hamster Syrian golden	Buccal mucous membrane brushing, 1 or 3 mg 3 times/week for 18 weeks	No tumors	Sunderman et al., 1978
Ni_3S_2	Hamster Syrian golden	Intramuscular, 5 or 10 mg, single	Sarcomas	Sunderman et al., 1978
N_3S_2 implanted in tracheas grafted under dorsal skin of isogenic recipients	Rat	1 or 3 mg Ni_3S_2/gelatin pellet implanted in tracheas 4 weeks post-grafting	10 percent carcinomas, 1 mg; 1.5 percent, 3 mg; 67 percent fibro-/myosarcomas, 3 mg	Yarita and Nettesheim, 1978
Hamster fetal cells transformed by Ni_3S_2 (0.1-1.0 μg/ml medium)	Nude mice	Subcutaneous injection	Sarcomas	Costa et al., 1979
Ni_3S_2	Mice NMRI	Intramuscular, subcutaneous, 10 mg	Local sarcomas in 11 of 16 (s.c.) and 6 of 16 (i.m.)	Oskarsson et al., 1979
Ni_3S_2	Rats Fischer	Intrarenal injections, 10 mg	Renal cancers in 18 of 24	Sunderman et al., 1979a
Ni_3S_2 injected into vitreous cavity of right eye	Rats (juvenile)	0.5 mg/rat	Malignant ocular tumors by 8 mo. in 14/15 treated rats	Sunderman et al., 1980

(continued on following page)

TABLE 8-14. (continued)

Nickel Compound	Animal	Route, Dose	Response	Reference
Ni_3S_2	Rats (pregnant)	Intramuscular injections on day 6	Local sarcomas in all dams, no excess tumors in progeny	Sunderman et al., 1981
α-Ni_3S_2	Rabbits Albino	Intramuscular implantation, 80 mg	Rhabdomyosarcomas, fibrosarcomas, leiomyosarcomas	Hildebrand and Tetaert, 1981
α-Ni_3S_2	Rats Fischer	Intraocular, 0.5 mg	Retinoblastomas, gliomas, and melanomas	Albert et al., 1982
Ni_3S_2	Rats Fischer and Hooded	Intramuscular	Rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas, and lymphosarcomas	Yamashiro et al., 1983
Ni_3S_2	Rats Wistar	Intramuscular, 40 µmol	Sarcomas	Kasprzak et al., 1983
Ni_3S_2	Rats	Intrapleural injection	Malignant tumors in the chest cavity, mostly rhabdomyosarcomas	Skaug et al., 1985

Agency for Research on Cancer (1976). When the data are taken in aggregate, it can be concluded that nickel subsulfide is carcinogenic in animals.

Studies comparing species and strain, route of administration, and organ sensitivity, as well as dose-response characteristics of nickel subsulfide carcinogenesis, have also been performed (Gilman and Yamashiro, 1985; Sunderman et al., 1979b, 1978; Hildebrand and Biserte, 1979a; Friedman and Bird, 1969; Daniels, 1966; Gilman, 1962). These data have been reviewed by Sunderman (1983) and Gilman and Yamashiro (1985), and are presented in Tables 8-15 through 8-18. While there are definite differences in tumor response between species/strain and route of administration, different experimental conditions among laboratories make cross comparison difficult. Gilman's analysis (Table 8-15) seems to indicate that rats are more susceptible than mice, rabbits, or hamsters. Sunderman (1983) indicates that absolute species susceptibility is difficult to rank because differences arise when experimental conditions or routes of administration differ. Sunderman (1983), in the same report, showed a definite dose-response relationship for tumor induction by nickel subsulfide following intrarenal and intramuscular injections (Table 8-18). Gilman and Yamashiro (1985) suggested a relative strain susceptibility ranking of Hooded > Wistar > Fischer > Sprague-Dawley rats when nickel subsulfide was administered intramuscularly (Table 8-16). Sunderman (1983), on the other hand, reported a relative strain susceptibility of Wistar > NIH Black > Fischer > Hooded, when nickel subsulfide was administered via the intrarenal route (Table 8-17). Comparison of the routes of administration on organ susceptibility of Fischer rats to nickel subsulfide carcinogenesis gave a relative ranking of eye > muscle > testis $\simeq$ kidney > liver (Sunderman, 1983; Table 8-18).

8.2.2.2 Nickel Metal. Powdered or pelleted metallic nickel has been tested for carcinogenic potential using different animal models and several routes of administration. Although the inhalation studies have not shown that nickel in the metallic form will produce respiratory tract tumors, Hueper's (1958) studies reported the observation of adenomatoid lung lesions in rats and bronchial adenomatoid lesions in guinea pigs. Furthermore, Hueper (1958) reported that an alveolar anaplastic carcinoma was found in one guinea pig lung, and a "metastatic lesion" (lymph node) was found in a second animal. As previously mentioned, however, this study has been criticized as no control animals were used. Several injection studies have shown the induction of malignant sarcomas at the site of administration, whereas others have shown no

TABLE 8-15. SPECIES DIFFERENCES TO NICKEL SUBSULFIDE: INTRAMUSCULAR INJECTION

Species and Dose (mg)		No. Animals (% Tumors)		Tumor Type (%) Rhabdomyosarcomas	Other
Syrian	(5)	15	(33)	20	80
Hamster[a]	(10)	17[1]	(71)	50	50
Mice[a]	(2.5)	20[2]	(55)	few	most
Mice[b]	(5)	45[3]	(60)	10	90
Rabbit[c]	(80)	16	(100)	most	few
Rat[d]	(5)	38	(92)	54	44
Rat	(10)	23	(96)		
Rat[e]	(10)	63	(94)	66	34

[1] DBA/2 and $C_{57}BL/6$; [2] C_3H and Swiss outbred
[3] Bilateral injections; exact numbers not stated

[a] Sunderman (1983); [b] Gilman (1962); [c] Hildebrand and Biserte (1979a); [d] Sunderman (1979); [e] Yamashiro et al. (1980).

Source: Gilman and Yamashiro (1985).

TABLE 8-16. STRAIN DIFFERENCES IN RATS TO NICKEL SUBSULFIDE: INTRAMUSCULAR INJECTION

Strain and Dose (mg)		% Tumors Sited	% Rhabdomyosarcomas	% Other Sarcomas
Sprague - Dawley	(20)[a]	37	82	18
Hooded	(10)	96	91	9
Fischer	(10)	78	87	13
Wistar	(10)	82	86	14

[a] Friedmann and Bird (1969)

Source: Gilman and Yamashiro (1985).

TABLE 8-17. STRAIN DIFFERENCES: CARCINOGENICITY OF NICKEL SUBSULFIDE AFTER A SINGLE INTRARENAL INJECTION IN FOUR RAT STRAINS

Rat Strain	Sex[a]	Dose (mg/rat)	Rats With Renal Tumors	Median Tumor Latent Period (mo)	Tumors With Distant Metastases	Survivors at End of Study	Median Survival Period (mo)
Long-Evans	M	5	0/6			4/6	>24
	F	5	0/6			4/6	>24
	M+F	5	0/12			8/12	>24
Fischer	M	5	5/18	11	1/5	9/18	23
	F	5	4/13	17	1/4	3/13	22
	M+F	5	9/31[b]	13	2/9	12/32	23
NIH Black	M	5	3/6	12	2/3	1/6	11
	F	5	3/6	10	3/3	3/6	12
	M+F	5	6/12[c]	11	5/6	4/12	11[b]
Wistar-Lewis	M	5	2/5	10	2/2	0/5	12
	F	5	5/6[c]	17	3/5	1/6	13
	M+F	5	7/11[c]	14	5/7	1/11[c]	13[b]

[a] M = male; F = female.

[b] $p < 0.05$ versus corresponding value for Long-Evans Hooded rats.

[c] $p < 0.01$ versus corresponding value for Long-Evans Hooded rats.

Source: Sunderman (1983).

TABLE 8-18. ROUTE OF ADMINISTRATION DIFFERENCES AND DOSE-RESPONSE: CARCINOGENICITY OF NICKEL SUBSULFIDE IN MALE FISCHER RATS

Route of Single Injection	Dose (mg/rat)	Rats With Local Tumors	Median Tumor Latent Period (mo)	Tumors With Distant Metastases	Survivors at End of Study	Median Survival Period (mo)
Intramuscular	0	0/142[a]			69/142	23
	0.6	7/29[a]	11	4/7	7/29	14
	1.2	23/30[a]	10	5/23	5/30[b]	15
	2.5	105/112[a]	10	37/105	2/112[a]	12[c]
	5.0	35/38[a]	7	17/35	1/38[a]	9[a]
	10.0	22/23[a]	6	27/22	0/23[a]	7[a]
	20.0	9/9[a]	7	6/9	0/9[a]	8[a]
Intrarenal	0	0/35			26/35	>24
	0.6	0/11			10/11	>24
	1.2	0/12			7/11	>24
	2.5	0/12			8/12	>24
	5.0	5/18[c]	11	1/5	9/18[b]	23
	10.0	18/24[a]	9	13/18	2/24[a]	14[a]
Intrahepatic	0	0/6			1/6	17
	5.0	0/13			3/13	18
	10.0	1/6	13	1/1	0/6	13
Intratesticular	0	0/18			10/18	18
	10.0	16/19[a]	10	4/16	0/19[c]	11[c]
Intraocular	0	0/11			d	
	0.5	14/15[a]	8	1/14	d	
Submaxillary gland	2.5	0/11			3/11	17

[a] $p < 0.001$ versus corresponding controls.

[b] $p < 0.05$ versus corresponding controls.

[c] $p < 0.01$ versus corresponding controls.

[d] The intraocular carcinogenesis study was terminated at 10 months.

Source: Sunderman (1983).

induction. The data are summarized in Table 8-19. Intrafemoral injections induced tumors in rats and rabbits (Hueper, 1955, 1952). Intravenous injections produced tumors in rats but not in rabbits and mice (Hueper, 1955). Intramuscular injection was the route most studied, and tumors were observed in rats and possibly hamsters but not in mice (Sunderman, 1984a; Jasmin et al., 1979; Sunderman and Maenza, 1976; Furst et al., 1973; Furst and Schlauder, 1971; Haro et al., 1968; Heath and Daniel, 1964; Hueper, 1955). Sunderman and Maenza (1976) observed a dose-response relationship between tumor formation and levels of nickel injected intramuscularly.

Based on the strong tumor response from intramuscular injection studies, and the observation (albeit somewhat questionable) of adenomatoid lesions of the respiratory tract from inhalation studies, metallic nickel should be considered as having carcinogenic potential in animals. However, tests are presently inadequate to support any definitive conclusions regarding its carcinogenicity.

As noted above, some species, strain, and route of administration differences were observed. Both the intramuscular and intravenous routes (Furst and Schlauder, 1971; Hueper, 1955) showed that rats are more susceptible than hamsters, rabbits, or mice. Sunderman and Maenza (1976) have observed a dose-response relationship using the intramuscular route of administration. The route of administration and tumor production seem to follow a ranking of intramuscular > intrapleural $\geq$ intrafemoral > intrarenal > intravenous.

8.2.2.3 Nickel Oxide. The carcinogenicity of nickel (II) oxide (NiO) in experimental animals has not been well studied. The inhalation studies have been reviewed in section 8.2.1.1 of this chapter. While the results of Wehner et al. (1975) showed no significant carcinogenic effects from nickel oxide exposures alone or in conjunction with cigarette smoke, it is difficult to determine if this was a consequence of the animal model used (Syrian golden hamsters). Horie et al. (1985) reported the observation of one lung adenocarcinoma out of 6 rats sacrificed 20 months after a 1-month exposure to 0.6 mg/m^3 of nickel oxide aerosol. The significance of this later study is uncertain because of the limitations of the experiment design. Intratracheal injection studies (Saknyn and Blohkin, 1978; Farrell and Davis, 1974) gave negative to equivocal results. However, nickel oxide was tested to be carcinogenic in five intramuscular injection studies (Suderman, 1984a; Gilman, 1966, 1965, 1962; Payne, 1964) with tumor incidence ranging from 5 to 93 percent, dependent upon the dose and species and strain of animal used. It should be noted that

TABLE 8-19. EXPERIMENTAL STUDIES OF NICKEL METAL CARCINOGENESIS

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Nickel metal (powder)	Mice	Inhalation, dose not given	Some tumors (no controls used)	Campell, 1943 as reviewed by Rigaut, 1983
Nickel metal (powder) 99% pure ($\leq 4 \mu m$)	Rats Wistar and NIH Black	Inhalation, 15 mg/m^3 6 hrs/day, 4-5 days/week for 2 years or over	No tumors 15/50 rats with adenomatoid lung lesions	Hueper, 1958
	Mice C57BL	"	2 lymphosarcomas in 20 mice	Hueper, 1958
	Guinea pigs	"	Bronchial adenomatoid lesions	Hueper, 1958
Nickel metal (powder)	Hamsters	Inhalation, level not specified	No tumors	Hueper and Payne, 1962
Nickel metal (powder)	Dogs	Inhalation, 5-6 mg/m^3 10 minutes/day for 6 months	No cancer (fibrosis only)	Selivanova and Ponomarkov, 1963 as reviewed by Rigaut, 1983
Nickel metal (dust)	Rats, albino (female)	Intratracheal injections, 10 mg Ni/rat	0/7	Mukubo, 1978 as reviewed by Sunderman, 1981
		10 mg Ni + 5 mg methylcholanthrene	3/5 squamous cell carcinomas	
Nickel metal (powder)	Rats Osborne-Mendal (female)	Intrapleural, 5 monthly injections of 0.5 ml of 12.5% (by volume) suspension	4/12 rats with injection site sarcomas	Hueper, 1952

(continued on following page)

TABLE 8-19. (continued)

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Nickel metal (powder)	Rats Osborne-Mendal	Intrafemoral, 21 mg (0.05 ml of a 12.5% by volume Ni suspension in lanolin)	4/17 rats with tumors 1 squamous cell carcinoma, 3 osteosarcomas	Hueper, 1952
	"	Intranasal	No tumors	Hueper, 1952
Nickel metal (powder)	Rats Wistar	Intrafemoral implant, 50 mg (0.1 ml of a 5% suspension in 20% gelatin in saline)	28% of treated rats with tumors of injected thighs, compared to 0% in control rats	Hueper, 1955
	Rabbits Dutch	Intrafemoral implant, 54 mg/kg (0.25 ml of a 12.5% by volume Ni in lanolin)	1/6 rabbits with fibrosarcomas	Hueper, 1955
	Mice C57BL	Intravenous, weekly for 2 weeks 0.05 ml of a 0.005% Ni in 2.5% gelatin	No tumors	Hueper, 1955
	Rabbits	Intravenous, 6 times of a 1% Ni suspension in 2.5% gelatin at a rate of 0.5 ml/kg	No tumors	Hueper, 1955
	Rats Wistar	Intravenous, 6 times of 0.5% Ni suspension in saline at 0.5 ml/kg	7/25 rats with tumors	Hueper, 1955
Nickel metal (powder)	Mice C57BL	Intraperitoneal, 0.02 ml of a 0.05% Ni suspension in 2.5% gelatin	No tumors	Hueper, 1955
	Mice C57BL	Intramuscular, 0.02 ml of a 0.05% Ni suspension in 2.5% gelatin	No tumors	Hueper, 1955
Nickel metal (pellet)	Rats Wistar	Subdermal implant, 4 pellets of 2 mm	5/10 rats, sarcomas around pellet	Mitchell et al., 1960

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TABLE 8-19. (continued)

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Nickel metal (powder)	Rats NIH Black	Intrapulmonary, 4 mg/rat	1/14 rats with sarcoma of injection site in 18 months	Hueper and Payne, 1962
Nickel metal (powder)	Rats Hooded (female)	Intramuscular, 28.3 mg in 0.4 ml fowl serum	10/10 rats with local rhabdomyosarcomas	Heath and Daniel, 1964
Nickel metal (powder)	Rats Fischer	Intramuscular, 50 mg	66% rats with sarcomas	Haro et al., 1968
Nickel metal (powder)	Rats Fischer	Intramuscular, 5 monthly injections of 5 mg Ni in 0.2 ml trioctanoin	38/50 rats with fibrosarcomas	Furst and Schlauder, 1971
	Hamsters	"	2/50 hamsters with fibrosarcomas	Furst and Schlauder, 1971
Nickel metal (powder)	Rats Fischer	Intrapleural, 5 monthly injections of 5 mg Ni in 0.2 ml saline	2/10 rats with pleural mesotheliomas	Furst et al., 1973
Nickel metal ([illegible]der)	Rats Fischer	Intramuscular, nickel in 0.5 ml penicillin G Procain		
		3.6 mg/rat 14.4 mg/rat	0/10 rats with local tumors 2/10 " " " "	Sunderman and Maenza, 1976
Nickel metal (powder)	Rats Sprague-Dawley	Intrarenal, 5 mg and 10 mg	No cancer of the kidney	Jasmin et al., 1979
Nickel metal (powder)	Rats Fischer	Intrarenal, 7 mg	0/18 rats with renal tumor	Sunderman et al., 1984
Nickel metal (powder)	Rats Fischer	Intramuscular, 14 mg	65% rats with sarcomas	Sunderman, 1984a

controls were not used in some of these studies. Nickel oxide was also carcinogenic by intrapleural injections, with an activity that approached that of nickel subsulfide (Skaug et al., 1985). It has not been tested to be carcinogenic by intrarenal injections (Sunderman et al., 1984). These data are summarized in Table 8-20. Taken together, the data support the evaluation of nickel oxide as having limited evidence as an animal carcinogen. Nickel(III) oxide (Ni_2O_3) has not been found to be carcinogenic in two intramuscular injection studies (Payne, 1964; Sosinski, 1975). However, the Sosinski (1975) study gave a marginal (2/40) tumor response by intracerebral injections.

8.2.2.4 Nickel Refinery Dusts. Nickel refinery flue dust ($\sim$20 percent $NiSO_4$, 57 percent Ni_3S_2, 6.3 percent NiO) was tested for carcinogenic potential by Gilman and Ruckerbauer (1962). They found the refinery flue dust to be a strong inducer of injection site sarcomas in rats and mice. According to a review by Rigaut (1983), Fisher et al. (1971) tested the carcinogenicity of refinery dust (59 percent Ni_3S_2, 20 percent $NiSO_4$, 6.3 percent NiO) in rats by inhalation. The refinery dust was one of 6 types of dust exposures administered to 348 rats, and 11 pulmonary tumors were observed for the combined refinery dust, synthetic dust, Ni_3S_2 and FeS groups. Kim et al. (1976) indicated the observation of 1 lung cancer in 60 rats exposed by inhalation to a combination of nickel and iron dusts.

Sunderman (1981) reviewed the carcinogenesis studies of nickel from 1975 to 1980 and reported on a study by Saknyn and Blohkin (1978), who used a feinstein dust (an intermediate product of nickel refining which contains NiS, NiO, and metallic nickel) at a level of 70 mg dust/m^3, 5 hours/day, 5 days/week for 6 months. Squamous cell carcinomas were found in two of five rats which survived the treatment. Saknyn and Blohkin (1978) also treated albino rats by intraperitoneal injections with feinstein dust at a dosage of 90 to 150 mg/rat. Six of 39 rats developed injection site sarcomas.

The Rigaut (1983) report also reviewed an inhalation study by Belobragina and Saknyn (1964) on rats exposed to nickel dust from roasting (31 percent Ni_3S_2, 33.4 percent NiO + SiO_2 and oxides of iron and aluminum). At 80 to 100 mg/m^3, 5 hours/day for 12 months, no tumors were found. A summary of these data is included in Table 8-21. The data seem to indicate that some nickel refinery dusts are potentially carcinogenic, but further studies are needed to more fully understand their carcinogenic activities.

TABLE 8-20. EXPERIMENTAL STUDIES OF NICKEL OXIDE CARCINOGENESIS

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Nickel oxide dust (NiO), 0.3 μm Baker Analyzed reagent	Hamsters Syrian golden (male) 5 animals/ group	1. Inhalation, 53.2 mg/m^3 life span exposure at 7 hr/day, 5 days/wk + sham-smoke 2. + cigarette smoke 10 minutes 2 x before and 1 after the 7 hr daily exposure 3. Sham-smoke + sham dust 4. Smoke + sham dust	2 osteosarcomas 2 osteosarcomas and 1 rhabdomyosarcoma	Wehner et al., 1975
Nickel oxide (NiO) aerosol Soekawa Chem Ind Japan	Rats Wistar, (male)	Inhalation, 0.6 mg/m^3 and 8 mg/m^3, 6 hrs/day, 5 days/wk for 1 month	1 pulmonary adenocarcinoma in 6 rats of the 0.6 mg/m^3 exposure group after 20 months.	Horie et al., 1985
Nickel Oxide (NiO) Merok, PA	Rats Wistar (male)	Intrapleural injection, 1 x 10 mg in 0.4 ml saline	31 of 32 rats with sarcomas (mostly rhabdomyosarcomas) after 30 months 5 of 32 rats with tumors in controls (no rhabdomyosarcomas)	Skaug et al., 1985
NiO (green-grey) Matheson, Coleman & Bell	Rats, Fischer 344 (male)	Intramuscular injection 14 mg Ni/rat in 0.3-0.5 ml 1:1 glycerol-water or procain penicillin G suspension	14 of 15 rats with sarcomas (~ 50% rhabdomyosarcomas)	Sunderman, 1984a
NiO (green)	Rats, Fischer 344 (male)	Intrarenal injection 7 mg Ni/rat in 0.1 or 0.2 ml of vehicle 0.14M NaCl (or glycerol) and water 1:1	No tumors observed in 12 rats	Sunderman et al., 1984

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TABLE 8-20. (continued)

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
NiO particles (0.5 to 1 µm)	Hamsters Syrian	Intratracheal, 30 wkly injections of 0.2 ml of a 2 g NiO in 100 ml 0.5% gelatin in saline (120 mg total)	1 respiratory tumor in 50 hamsters compared with 4 in 50 carbon dust group	Farrell and Davis, 1974
NiO	Mice Swiss	Intramuscular implant, 5 mg	5 rhabdomyosarcomas and 16 fibrosarcomas in 50 mice (no controls used)	Gilman, 1965
NiO	Rats, Wistar Mice, Swiss Rats, Fischer	Intramuscular, 20-30 mg " 5 mg " 20-30 mg	65% rats with sarcomas 66% " " 5% " "	Gilman, 1966
NiO	Rats NIH Black	Intramuscular implants, 7 mg	4 sarcomas in 35 rats after 18 months	Payne, 1964
NiO	Rats Wistar	Intramuscular injection, 20 mg	26 local tumors in 32 rats (80%) (no controls used)	Gilman, 1962
NiO	Mice Swiss	Intramuscular injection, 5 mg	35% mice with tumors	Gilman, 1962
NiO	Mice C3H	Intramuscular injection, 5 mg	23% mice with tumors	Gilman, 1962
NiO	Rats albino	Intratracheal, 20 to 40 mg/rat	1/20 rats with squamous cell carcinomas	Saknyn and Blohkin, 1978 as reviewed by Sunderman, 1981
Ni_2O_3 (black oxide)	Rats NIH Black	Intramuscular implant, 7 mg	0/35 after 18 months	Payne, 1964
Ni_2O_3 (black oxide)	Rats Wistar (male and female)	Intramuscular implant, 10 mg Intracerebral, 3 mg	No tumors in 20 male and 20 female rats 1 sarcoma, 1 meningioma	Sosinski, 1975

TABLE 8-21. EXPERIMENTAL CARCINOGENESIS STUDIES OF NICKEL REFINERY AND OTHER DUSTS

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Nickel refinery flue dust (20% $NiSO_4$, 57% Ni_3S_2, 6.3% NiO) (Source: Port Colborne, Canada)	Rats	Intramuscular, 20 or 30 mg one or both thighs		
	Hooded		52/66 rats with sarcomas	Gilman and Ruckerbauer, 1962
	Wistar		8/20 rats with sarcomas	
	Mice	Intramuscular, 10 mg each thigh	23/40 mice with sarcomas	Gilman and Ruckerbauer, 1962
Refinery dust (59% Ni_3S_2, 20% $NiSO_4$, 6.3% NiO)	Rats	Inhalation, 5-15 mg/m^3	11 pulmonary tumors in refinery dust, synthetic dust Ni_3S_2, FeS groups	Fisher et al., 1971 as reviewed by Rigaut, 1983
Nickel refinery dust (24.1% $NiSO_4$, 68.7% Ni_3S_2, 7.2% NiO) metallic nickel dust, hematite, and pyrrhotite	Rats Wistar	Inhalation, 2.1 ± 0.2 mg Ni/m^3, 1.9 ± 0.2 mg Fe/m^3	1/60 rats with lung cancer	Kim et al., 1976
Nickel dust from roasting (31% Ni_3S_2, 33.4% NiO + SiO_2 and oxides of iron and aluminum)	Rats	Inhalation, 80-100 mg/m^3 5 hrs/day, 12 months	No cancers	Belobragina and Saknyn, 1964 as reviewed by Rigaut, 1983
Dust from electric furnace (95% NiO)	Rats	Inhalation, 80-100 mg/m^3 5 hrs/day, 12 months	No cancers	Belobragina and Saknyn, 1964 as reviewed by Rigaut, 1983
Feinstein dust	Rats (albino, nonpedigree)	Inhalation, 70 mg dust/m^3 5 hrs/day, 5 days/wk for 6 months	2 of 5 surviving rats with squamous cell carcinomas	Saknyn and Blohkin, 1978 as reviewed by Sunderman, 1981
		Intraperitoneal injection 90-150 mg dust/rat	6/39 rats with injection site sarcomas	Saknyn and Blohkin, 1978 as reviewed by Sunderman, 1981

8.2.2.5 Soluble and Sparingly Soluble Nickel Compounds. The soluble nickel compounds--nickel sulfate ($NiSO_4$), nickel chloride ($NiCl_2$), and nickel acetate ($Ni(CH_3OO)_2$)--have received a limited amount of study, and the findings are summarized in Table 8-22.

Nickel acetate was studied for carcinogenic potential by Stoner et al. (1976), Schroeder et al. (1974, 1964), Haro et al. (1968), and Payne (1964). Haro et al. (1968) observed that 22 percent of the rats developed sarcomas when injected intramuscularly with nickel acetate. The observation of lung adenomas and adenocarcinomas (significant for the 360-mg/kg group) in Strain A mice receiving intraperitoneal injections are particularly interesting because the observation indicates the potential of soluble nickel compounds in inducing tumors in animals. However, the validity of using lung tumor response data in Strain A mice as an indicator of carcinogenicity is uncertain. Other injection studies have shown negative results, and the drinking water studies of Schroeder et al. (1964) and Schroeder and Mitchener (1975) are inadequate to draw any firm conclusions.

Another soluble nickel compound, nickel sulfate, has been tested, mainly via the intramuscular route (Kasprzak et al., 1983; Gilman, 1966, 1962; Payne, 1964), and no treatment-related tumors have been observed. Payne (1964) did report 1 sarcoma of 35 rats receiving nickel sulfate by muscle implant. In the only ingestion study by Ambrose et al. (1976), no tumors were observed in rats or dogs.

Payne (1964) is the only investigator to have studied the carcinogenesis of nickel chloride using muscle implants. None of the 35 NIH black rats receiving 7 mg of nickel chloride developed sarcomas.

For the sparingly soluble nickel compounds, both nickel carbonate ($NiCO_3$) (Payne, 1964) and nickel hydroxide ($Ni(OH)_2$) in the crystalline, dried, and colloidal forms have been studied (Kasprzak et al., 1983; Gilman, 1966, 1965). Payne (1964) observed 4 of 35 rats with sarcomas after muscle implants of 7 mg nickel carbonate/rat.

Gilman (1966, 1965) observed the development of local sarcomas in 48 percent of rats receiving nickel hydroxide (form not specified) intramuscularly. Kasprzak et al. (1983) further studied the effect of the physical state of nickel hydroxide on carcinogenic activities and found that intramuscular injection of 120 μmole of the dried gel gave a higher yield of sarcomas as compared to crystalline nickel hydroxide. The colloidal form produced no sarcomas.

TABLE 8-22. EXPERIMENTAL CARCINOGENESIS STUDIES OF SOLUBLE AND SPARINGLY SOLUBLE NICKEL COMPOUNDS

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Nickel acetate [$Ni(CH_3COO)_2$]	Rats Fischer	i.m. injections, 35 mg/kg monthly for 4-6 months (trioctanoin as vehicle)	22% rats with sarcomas	Haro et al., 1968 as reviewed by Rigaut, 1983
$Ni(CH_3COO)_2 \cdot 4H_2O$	Rats NIH Black	i.m. implant, 7 mg	1/35 rats with sarcomas	Payne, 1964
$Ni(CH_3COO)_2$ anhydrous	Rats NIH Black	i.m. implant, 7 mg	0/35	Payne, 1964
$Ni(CH_3COO)_2$	Mice Swiss	Ingestion (drinking water), 5 ppm	No treatment-related tumors	Schroeder et al., 1964 Schroeder and Mitchener, 1975
$Ni(CH_3COO)_2$	Mice Strain A	Intraperitoneal, 24 injections 3/week at 72,180,360 mg/kg	Lung adenomas and adenocarcinomas (significant for 360 mg/kg group)	Stoner et al., 1976
Nickel sulfate $NiSO_4$	Rats Wistar	i.m. injection, 5 mg	No tumors	Gilman, 1962
$NiSO_4$	Rats Fischer	i.m. injection	No tumors	Gilman, 1966 as reviewed by Rigaut, 1983
$NiSO_4$	Rats NIH Black	Muscle implant, 7 mg	1/35 rats with injection site sarcomas	Payne, 1964
$NiSO_4$	Rats Wistar	i.m. injection, 66 μmole/rat 15 x 4.4 μmole doses	0/20	Kasprazak et al., 1983
Nickel sulfate $NiSO_4 \cdot 6H_2O$	Rats Wistar	Ingestion in solid food	No tumors	Ambrose et al., 1976
" "	Dogs beagle	0,100,1000 and 2500 nickel as nickel sulfate	0/6 dogs with tumors from all dosage groups	Ambrose et al., 1976

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TABLE 8-22. (continued)

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
$NiCl_2$	Rats NIH Black	Muscle implant, 7 mg	0/35	Payne, 1964 as reviewed by IARC, 1976
$NiCO_3$	Rats NIH Black	Muscle implant, 7 mg	4/35 injection site sarcomas	Payne, 1964
Nickel hydroxide (form not specified)	Rats Wistar	i.m. injections, bilateral 5 mg/thigh	48% local sarcomas (19 of 40 sites)	Gilman, 1966, 1965 as reviewed by Rigaut, 1983 or Gilman and Yamashiro, 1985
"	Rats Fischer	"	"	"
$Ni(OH)_2$, air dried gel	Rats Wistar	i.m., 120 µmole	5/19 rats with sarcomas (2 metastasis to lung)	Kasprzak and Poirier, 1985
$Ni(OH)_2$ crystalline	Rats Wistar	i.m., 120 µmole	3/20 rats with sarcomas (1 metastasis to lung)	Kasprzak and Poirier, 1985
$Ni(OH)_2$ colloidal	Rats Wistar	i.m., 120 µmole	0/13	Kasprzak and Poirier, 1985

The data seem to indicate that both soluble and sparingly soluble nickel compounds have the potential to induce tumors in animals, but these compounds have not been adequately tested to support a judgment of their carcinogenicity.

8.2.2.6 Specialty Nickel Compounds. Nickelocene is used as a laboratory reagent. It has been studied only in regard to intramuscular injection (Furst and Schlauder, 1971; Haro et al., 1968). Fibrosarcomas, in particular, were observed in rats and hamsters in these studies (see Table 8-23).

Nickel carbonyl was used as an intermediate in the refining of nickel by the Mond process (International Agency for Research of Cancer, 1976), but it is also a specialty reagent for the fabrication of nickel alloys and in the manufacture of catalysts. Nickel carbonyl has been tested by inhalation (Sunderman and Donnelly, 1965; Sunderman et al., 1959, 1957) to be carcinogenic, producing lung neoplasms. Because of the high toxicity of nickel carbonyl, the testing regimen was around the LD_{50} and mortality was high. The intravenous injection study by Lau et al. (1972) produced malignant tumors at various sites. Taken together, these studies show sufficient evidence that nickel carbonyl is carcinogenic to animals.

8.2.2.7 Potentiations and Inhibitions of Nickel Carcinogenesis. In addition to the studies of the carcinogenicity of nickel compounds, studies to investigate the potential for synergism and antagonism were also performed. Maenza et al. (1971) observed that nickel subsulfide, co-administered with benzpyrene, significantly reduced (30 percent) the latency period for sarcoma induction by the intramuscular route. Kasprzak et al. (1973) studied the effects of co-administering nickel subsulfide and benzpyrene to rats by intratracheal injections. They found that none of the rats receiving nickel subsulfide alone developed bronchial metaplasia, while 62 percent of rats receiving nickel subsulfide and benzpyrene and 31 percent of those receiving benzpyrene alone developed bronchial metaplasia.

Sunderman et al. (1976, 1975) observed a dramatic reduction of sarcomas (from 73 percent to 7 percent) in Fischer rats when manganese powder was co-administered with nickel subsulfide by intramuscular injections. Furthermore, Sunderman et al. (1979a) observed the inhibitory effects of manganese on nickel subsulfide carcinogenesis by intrarenal injections. The results of the intrarenal injection study were less dramatic, however (from 75 to 32 percent). Kasprzak and Poirier (1985) found that basic magnesium carbonate was inhibitory

TABLE 8-23. EXPERIMENTAL CARCINOGENESIS STUDIES OF SPECIALTY NICKEL COMPOUNDS

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
$Ni(CO)_4$	Rats Wistar	Inhalation, 1 x 30 minutes of 0.6 mg/l or 3 x 30 minutes/wk for life 0.03 mg/l	1/35 rats with pulmonary adenocarcinomas, with metastases that survived 2 yrs or more 1/8 rats with pulmonary adenocarcinomas with metastases that survived 2 yrs or more; 0/44 in control	Sunderman and Donnelly, 1965
$Ni(CO)_4$	Rats Wistar (male)	Inhalation, 3 x 30 min/wk for 12 months 0.03 mg/l, 64 rats 0.06 mg/l, 32 rats 1 x 0.25 mg/l, 80 rats controls, 41 rats	4 exposed/ 9 surviving lung neoplasm; 2 from single exposure group 0/3 surviving in controls	Sunderman et al., 1957, 1959
$Ni(CO)_4$	Rats Sprague-Dawley	i.v., 6x50 µl/kg (9 mg Ni/kg)	19/121 rats with malignant tumors at various sites, 2/47 rats with pulmonary lymphomas ($p < 0.05$)	Lau et al., 1972
Nickelocene	Rats	Intramuscular	Sarcomas	Haro et al., 1968
	Hamsters	Intramuscular	Sarcomas	Haro et al., 1968
Nickelocene	Rats Fischer	i.m. injections, 12x12 mg nickelocene in 0.2 ml trioctanoin or 12x25 mg nickelocene in 0.2 ml trioctanoin	18/50 rats with fibrosarcomas 21/50 rats with fibrosarcomas 0/50 in controls	Furst and Schlauder, 1971
Nickelocene	Hamsters	i.m. injections, 1x25 mg nickelocene in 0.2 ml trioctanoin or 8x5 mg nickelocene in 0.2 ml trioctanoin	4/29 hamsters with fibrosarcomas No tumors	Furst and Schlauder, 1971

to the production of injection site sarcomas by nickel subsulfide in rats. Calcium carbonate was ineffective in the same experiment. Nickel oxide and metallic nickel were also investigated for synergistic effects with polycyclic aromatic hydrocarbons. The results of these studies are summarized in Table 8-24.

The results of the studies on nickel subsulfide indicate the synergistic and antagonistic effects of nickel subsulfide when combined with other agents. The results for nickel oxide and metallic nickel are, however, inadequate to draw any firm conclusions.

8.2.3 Physical, Chemical, Biological, and Toxicological Correlates of Carcinogenic Activities

In addition to epidemiologic and animal studies, investigations have been conducted in an attempt to correlate the physical, chemical, and biological properties of nickel compounds with carcinogenic activities. In order to compare the relative carcinogenic activities of different nickel compounds, the following section summarizes studies on the chemical and biological indices related to carcinogenicity.

8.2.3.1 Solubilization of Nickel Compounds. In a study with nickel (II) hydroxides and nickel (II) sulfate, Kasprzak et al. (1983) found an inverse relationship between carcinogenic activity and dissolution kinetics in human serum, artificial lung fluid, and ammonium acetate buffer. Groups of male Wistar rats received intramuscular injections of nickel compounds. The predominant tumors observed were injection site pleomorphic rhabdomyosarcomas. Frank hematuria was observed in all of the rats dosed with colloidal nickel (II) hydroxide, and seven of these animals died during the first two months of the study. One rat receiving air-dried nickel (II) hydroxide died with hematuria during the first week of the study. Histological examination of the kidneys of the rat revealed acute renal inflammation with numerous foci of glomerular and tubular necrosis. The dissolution rates of the compounds tested were different in the three media used, but the order of the dissolution rates was inversely related to carcinogenic activity.

Cellular uptake and solubilization of particulate nickel compounds appears to play an important mechanistic role in nickel-induced carcinogenesis. Costa and Mollenhauer (1980b) have shown that crystalline nickel subsulfide is actively phagocytized by cultured Chinese hamster ovary (CHO) and Syrian

TABLE 8-24. POTENTIATIONS AND INHIBITIONS OF NICKEL COMPOUNDS WITH OTHER AGENTS

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
Ni_3S_2 + benzpyrene (BP)	Rats	Intramuscular, 10 mg Ni_3S_2 ± 5 mg BP	100% rats with tumors all groups, Ni_3S_2 + BP group has a 30% latency reduction compared to Ni_3S_2 alone	Maenza et al., 1971
Ni_3S_2 + benzpyrene (BP)	Rats	Intratracheal, 5 mg Ni_3S_2 ± 2 mg BP		
		Ni_3S_2 alone	0/13 (0%) rats with bronchial metaplasia	Kasprzak et al., 1973
		BP alone	4/13 (31%)	
		Ni_3S_2 + BP	8/13 (62%)	
Ni_3S_2 + manganese	Rats Fischer	Intramuscular, 1.2 mg Ni_3S_2 ± 1 mg Mn powder		
		Ni_3S_2 alone	22/30 (73%) rats with sarcomas	Sunderman et al., 1975, 1976
		Ni_3S_2 + Mn	1/14 (7%)	
		Mn alone	0/14	
		Controls	0/39	
Ni_3S_2 + manganese	Rats Fischer	Intrarenal, 10 mg Ni_3S_2 ± 6.9 mg Mn		
		Ni_3S_2 alone	75% rats with carcinomas of kidney	Sunderman et al., 1979a
		Ni_3S_2 + Mn	32% rats with carcinomas of kidney	
Ni_3S_2 + magnesium	Rats Fischer	Intramuscular, 2.5 mg Ni_3S_2 ± 6.3 mg (4 $MgCO_3 \cdot Mg(OH)_2 \cdot nH_2O$; 40.6% MgO; $MgCO_3$)	Injection site sarcomas	Kasprzak and Poirier, 1985
		Ni_3S_2 alone	70-90% rats with tumors	
		Ni_3S_2 + magnesium basic carbonate	25% " " "	

(continued on following page)

TABLE 8-24. (continued)

Nickel Compound	Animal	Route, Dose	Tumor Response	Reference
NiO + methylcholanthrene	Rats (albino)	Intratracheal, dosage not given	5/30 rats with tumors	Toda, 1962
NiO + diethylnitrosourea (DENU)	Hamsters Syrian golden	Intratracheal, 4 mg NiO wkly for 30 weeks, 0.25mg DENU subcutaneously weekly for 12 weeks		
		NiO alone	0 rats with nasal tumors	Farrell and Davis, 1974
		DENU alone	3/200 " " " "	
		NiO + DENU	4/50 " " " "	
		Controls	0 " " " "	
NiO + smoke	Hamsters Syrian golden (51 animals/group)	Inhalation, 53.2 mg/m^3 ± cigarette smoke	No effect	Wehner et al., 1975
		NiO + sham smoke	2 osteosarcomas	
		NiO + cigarette smoke	2 osteosarcomas + 1 rhabdomyosarcoma	
		Sham dust + sham smoke	no tumors	
		Sham dust + cigarette smoke	no tumors	
Nickel metal (powder) + methylcholanthrene (MC)	Rats (albino)	Intratracheal, 10 mg Ni ± 5mg MC		
		Ni alone	0 rats with epidemoid tumor	Mukubo, 1978 as reviewed by Sunderman, 1981
		MC alone	2/7 " " " "	
		Ni + MC	3/5 " " " "	
Nickel metal + fly ash (FA)	Hamsters Syrian golden	Inhalation, 6 hrs/day, 5 days/wk for 4-14 wks nickel enriched fly ash (NEFA)		
		NEFA 17 mg/m^3	4 cancers (none pulmonary)	Wehner et al., 1981
		NEFA 70 mg/m^3	3 cancers (2 pulmonary)	
		FA 70 mg/m^3	3 cancers (none pulmonary)	
		Controls	4 cancers (none pulmonary)	
$NiSO_4$ + ethylnitrosourea (ENU)			Increased tumor obtained by ENU	Ivankovic and Zeller 1972 Zeller and Ivankovic, 1972 as reviewed by Rigaut, 1983

hamster embryo (SHE) cells. In contrast, no active phagocytosis was observed in cells exposed to amorphous nickel monosulfide. Costa et al. (1981b) observed phagocytized nickel particles in the cytoplasm of CHO and SHE cells. These particles were solubilized to a form capable of entering the nucleus and interacting with nuclear macromolecules (Costa et al., 1981b).

The effect of particle size on the toxicity and phagocytosis of metal compounds further substantiates the hypothesis that the biological effects of insoluble metal compounds are preceded by, and are probably dependent on, phagocytosis. Costa et al. (1981a) showed that particles of crystalline nickel monosulfide having mean diameters of 2 to 4 µm were phagocytized six times more than nickel monosulfide particles having mean diameters of 5 to 6 µm. In contrast, the size of the particle had no effect on the phagocytosis of amorphous nickel monosulfide. Studies by Costa and Mollenhauer (1980a,b) demonstrate that crystalline cobalt monosulfide is similarly a potent inducer of morphological transformation in CHO cells, while amorphous cobalt monosulfide lacks such activity. Since crystalline cobalt monosulfide is actively phagocytized and amorphous cobalt monosulfide is not, these results tend to support the effects noted with nickel and may be characteristic of other metals as well.

The crystal structure of the nickel compounds appears to be one of the factors affecting the biological activity of these compounds. Costa et al. (1981a) studied seven particulate nickel compounds in regard to their ability to induce morphological transformations in SHE cells and to phagocytize in CHO cells. Crystalline nickel subsulfide, nickel monosulfide, and nickel subselenide were significantly more active in inducing cell transformations and were more actively phagocytized than amorphous nickel monosulfide, metallic nickel, nickel (III) oxide, and nickel oxide. Intracellular uptake and distribution of crystalline nickel monosulfide particles appear to occur by normal endocytic and saltatory processes during the formation and breakdown of macropinosomes. Using time-lapse video microscopy, Evans et al. (1982) recorded the endocytosis and intracellular distribution of crystalline nickel monosulfide in CHO cells. Crystalline nickel monosulfide particles were phagocytized by CHO cells in regions of membrane ruffling. While these particles remained bound to the cell surface for periods ranging from minutes to hours, cellular uptake generally required only seven to ten minutes. Endocytosed crystalline nickel monosulfide particles exhibited saltatory motion. Lysosomes were observed to repeatedly interact with the nickel monosulfide particles in a manner similar to the digestion of macropinosomes. Nickel monosulfide particles were never observed to be exocytosed from the CHO cells. Over time, most of the particles aggregated to the region of the nucleus, with vacuoles forming around the particles. The observed lysosomal interaction with phagocytized cytoplasmic nickel monosulfide may accelerate dissolution of particulate nickel, allowing the entry of ionic nickel into the nucleus. Studies by Abbracchio et al. (1982) suggest that the dissolution of phagocytized crystalline nickel monosulfide particles is accelerated by several cytoplasmic events. Lysosomal interaction appears to be the most predominant factor, since the acidic pH of lysosomes could enhance the dissolution of crystalline nickel monosulfide particles.

Kuehn and Sunderman (1982) determined the dissolution half-times of 17 nickel compounds in water, rat serum, and renal cytosol. Concentrations of dissolved nickel were analyzed by electrothermal atomic absorption spectrophotometry, and dissolution half-times were computed using a Weibull distribution. Nickel, NiS, amorphous NiS, Ni_3S_2, NiSe, Ni_3Se_2, NiTe, NiAs, $Ni_{11}As_8$, Ni_5As_2, and Ni_4FeS_4 dissolved more rapidly in serum or cytosol than in water. No detectable dissolution was observed for NiO, NiSb, NiFe alloy, or $NiTiO_3$ in any of the media. The dissolution half-times of nickel subsulfide in serum and cytosol are in close agreement with the excretion half-time of 24 days in urine following intramuscular injection of $^{63}Ni_3S_2$ in rats (Sunderman et al., 1976). These data suggest that in vitro dissolution half-times of nickel compounds may be used to predict in vivo excretion half-times, since the dissolution process is the rate-limiting step of distribution and excretion.

8.2.3.2 Phagocytosis of Nickel Compounds. Costa et al. (1982) reported that crystalline nickel monosulfide particles were actively phagocytized and induced morphological transformation in Syrian hamster embryo (SHE) cells in a concentration-dependent manner. In contrast, amorphous nickel monosulfide was not actively phagocytized by SHE cells and was relatively inactive in inducing morphological transformation at both cytotoxic and noncytotoxic concentration levels. Chemical reduction of positively charged amorphous nickel monosulfide with lithium aluminum hydride ($LiAlH_4$) resulted in active phagocytosis and increased morphological transformation of exposed SHE cells. In experiments with Chinese hamster ovary (CHO) cells, Costa et al. (1982) found that only crystalline, not amorphous, nickel monosulfide caused strand breaks in DNA. Phagocytized inert particles such as latex beads did not induce transformation or DNA damage, suggesting that genotoxic dissolution products such as nickel II, rather than the phagocytized particles, are responsible for the observed cellular transformation and damage to DNA. In these experiments, nickel chloride was one-third to one-half as potent in inducing cellular transformation as compared to crystalline nickel monosulfide on a weight basis. These results suggest a correlation between selective phagocytosis of nickel compounds and their ability to induce cellular transformation.

Entry of nickel sulfide particles into cells appears to be related to surface charge and to the degree of negative charge on the surface microenvironment. Heck and Costa (1982) found that the incidence of morphological transformation of SHE cells following exposure to crystalline nickel monosulfide particles was significantly greater than that following a similar exposure to amorphous nickel monosulfide particles. They attributed the differences in potency to the selective phagocytosis of crystalline nickel monosulfide particles into the SHE cells, since no uptake of amorphous nickel monosulfide was observed. Chemical reduction of amorphous nickel monosulfide and lithium aluminum hydride resulted in an increase in phagocytic uptake by CHO cells and an increase in morphological transformation in SHE cells. The phagocytosis and morphological transforming activity of crystalline nickel monosulfide was also increased by reduction with lithium aluminum hydride. These results are consistent with the hypothesis that the transforming activity of particulate metal compounds is proportional to their uptake by phagocytosis. Studies by Abbracchio et al. (1982, 1981) have demonstrated that crystalline nickel monosulfide particles have a negative surface potential (-28 mV), while amorphous nickel monosulfide particles have a positive surface charge (+9 mV). The negative surface charge of crystalline nickel monosulfide appears to be directly related to cellular uptake by phagocytosis. The extent of phagocytosis of crystalline nickel monosulfide particles is not affected by the components of the tissue culture medium used (Abbracchio et al., 1981). Altering the particle surface of both crystalline and amorphous nickel monosulfide by reduction with lithium aluminum hydride enhanced phagocytosis by CHO cells and, in the case of amorphous nickel monosulfide, resulted in induction of morphological transformation of SHE cells. Heck and Costa (1983) have found that crystalline nickel monosulfide, nickel subsulfide, and nickel oxide, which are carcinogenic by the intramuscular injection route, exhibit strongly negative surface charges in distilled water and enter CHO cells readily by phagocytosis. Under similar experimental conditions, amorphous nickel monosulfide, which appears to be noncarcinogenic, is positively charged and not extensively phagocytized. The greater dissolution rate of amorphous nickel monosulfide, in comparison to crystalline nickel monosulfide, may contribute to its reduced cellular uptake, due to alteration of the particle surface or generation of dissolution products which inhibit cellular uptake.

Maxwell and Nieboer (1984) reported that the ranking of eight nickel substances (size <10 μm, with known X-ray patterns) according to hemolytic ability correlated with the external roughness of the particulates as characterized by scanning electron microscopy. Ranking (at $p < 0.025$) of the materials by human serum albumin adsorption (given as μg/mg in parentheses) yielded a similar reaction sequence: colloidal $Ni(OH)_2$ (568 ± 13) > NiO (8.0 ± 0.5) > Ni powder, non-spherical and rough (4.3 ± 0.4) > αNiS, βNiS (3.4 ± 0.2); dried $Ni(OH)_2$ (2.9 ± 0.1); αNi_3S_2 (2.2 ± 0.4) > Ni powder, smooth spheres (0.4 ± 0.1). The authors concluded that surface passivity of relatively insoluble nickel compounds might be an important determinant in nickel carcinogenesis.

Kuehn et al. (1982) measured the relative phagocytosis of 17 nickel compounds in vitro in monolayer cultures of rat peritoneal macrophages. The macrophages were exposed to nickel particles (median diameter 1.5 μm) at concentrations of 2 μg/ml of medium for 1 hour at 37°C. The phagocytic index, the percentage of macrophages with one or more engulfed particles, ranged from 69 percent for nickel oxide to 3 percent for amorphous nickel monosulfide. In order of decreasing phagocytic indices, the 17 nickel compounds were ranked: $NiO > Ni_4FeS_4 > NiTiO_3 > NiSe > Ni_3S_2 > Ni > Ni_5As_2 > NiS_2 >$ NiFe alloy $> NiSb > Ni_{11}As_8 > Ni_3Se_2 > NiS > NiTe > NiAs > NiAsS >$ amorphous NiS. Rank correlation ($p < 0.03$) was observed between the relative phagocytic indices of the nickel compounds and their dissolution half-times in rat serum (Table 8-25). The biological data are summarized in Table 8-26. Data from carcinogenicity bioassays of 18 of the compounds tested in vitro do not exhibit any rank correlation between the phagocytic indices of nickel compounds and the incidences of injection site sarcomas after intramuscular administration to rats (Sunderman, 1984a). These data are summarized in Table 8-27.

Costa et al. (1981b) performed X-ray fluorescence spectrometry measurements of metal levels in subcellular fractions isolated from CHO cells treated with crystalline nickel subsulfide, crystalline nickel monosulfide, and amorphous nickel monosulfide. Amorphous nickel monosulfide did not significantly

TABLE 8-25. RANK-CORRELATIONS BETWEEN CHEMICAL AND BIOLOGICAL PARAMETERS OF NICKEL COMPOUNDS

Parameters Compared by Rank	No. of Compounds Compared	Kendall Correlation Coefficient	Z-Score[a]	P
Sarcoma incidence[b] versus:				
nickel mass-fraction[c]	18	0.35	2.0	0.02
serum T_{50}[d]	16	0.07	0.39	-
cytosol T_{50}[d]	16	0.11	0.62	-
phagocytic index[e]	17	0.17	0.93	-
hematocrit[f]	17	0.72	4.0	<0.0001
Hematocrit[f] versus:				
nickel mass-fraction[c]	17	0.51	2.5	<0.01
serum T_{50}[d]	16	0.06	0.35	-
cytosol T_{50}[d]	16	0.08	0.44	-
phagocytic index[e]	17	0.32	1.8	0.04
Phagocytic index[e] versus:				
nickel mass-fraction[c]	17	0.15	0.87	-
serum T_{50}[d]	16	0.35	1.9	0.03
cytosol T_{50}[d]	16	0.28	1.5	-
Nickel mass-fraction[b] versus:				
serum T_{50}[d]	16	-0.17	0.92	-
cytosol T_{50}[d]	16	-0.09	0.58	-
Serum T_{50}[d]				
Cytosol T_{50}[d]	16	0.79	4.3	<0.0001

[a] Correlation coefficient divided by its standard error.

[b] Sarcoma incidence in rats at two years after i.m. injection (14 mg Ni/rat).

[c] Proportional weight of nickel per unit weight of substance.

[d] Dissolution half-time during in vitro incubation at 37°C (2 mg Ni/ml).

[e] Phagocytosis by rat peritoneal macrophages in vitro (10 µg/ml).

[f] Mean blood hematocrit of rats at two months after i.r. injection (7 mg Ni/rat).

Souce: Sunderman (1984a).

TABLE 8-26. BIOLOGICAL CHARACTERISTICS OF NICKEL COMPOUNDS

Compound	Formula	Dissolution half-time in rat serum	Dissolution half-time in renal cytosol[a]	Phagocytic index in rat macrophages[b]	Hematocrit of rats after i.r. injection[c]
Nickel dust	Ni	>11 years	8.4 years	19.5± 5.9	67± 8[d]
Nickel oxide	NiO	>11 years	>11 years	69.0± 18.4	72± 11[d]
Nickel disulfide	NiS_2	FP[e]	FP[e]	16.5± 6.2	66± 9[d]
Nickel monosulfide	βNiS	2.6 years	1.4 years	7.4± 6.9	71± 7[d]
Nickel monosulfide	Amorphous NiS	24 days	19 days	3.4± 2.4	48± 1
Nickel subsulfide	αNi_3S_2	34 days	21 days	28.4± 6.3	74± 3[d]
Nickel monoselenide	NiSe	1.1 years	161 days	32.0± 6.1	71± 8[d]
Nickel subselenide	Ni_3Se_2	50 days	88 days	8.0± 4.4	67± 7[d]
Nickel telluride	NiTe	7.9 years	171 days	6.3± 5.2	49± 2
Nickel sulfarsenide	NiAsS	1.0 years	1.1 years	4.3± 2.2	61± 7[d]
Nickel monoarsenide	NiAs	46 days	14 days	4.8± 5.9	49± 2
Nickel subarsenide	$Ni_{11}As_8$	246 days	20 days	8.8± 2.1	50± 1
Nickel subarsenide	Ni_5As_2	73 days	110 days	17.3± 5.4	50± 2
Nickel antimonide	NiSb	>11 years	>11 years	13.0± 3.2	49± 2
Nickel ferrosulfide	Ni_4FeS_4	4.5 years	329 days	43.8± 10.0	70± 4[d]
Nickel alloy	$NiFe_{1.6}$	>11 years	>11 years	16.3± 6.2	49± 1
Nickel titanate	$NiTiO_3$	>11 years	>11 years	36.5± 7.5	49± 2
Nickel chromate	$NiCrO_4$	ND[f]	ND[f]	ND[f]	ND[f]

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[a] The dissolution half-time represents the estimated time for dissolution of 50% of nickel-containing particles in rat serum or renal cytosol during *in vitro* incubation (37°C, 2 mg Ni/ml) (Kuehn and Sunderman, 1982).

[b] The phagocytic index represents the percentage (mean ± SD) of rat peritoneal macrophages that phagocytized one or more particles during incubation for 1 h at 37°C in medium that contained nickel compounds (10 μg/ml) (Kuehn et al., 1982).

[c] Blood hematocrit (%, mean ± SD) in groups of 11-57 rats at two months after intrarenal injection of nickel compounds (7 mg Ni/rat). The corresponding mean hematocrit in 79 control rats at two months after intrarenal injection of vehicle was 49 ± 3% (Sunderman and Hopfer, 1983).

[d] $p < 0.01$ versus vehicle controls.

[e] Formation of flocculent precipitates (FP) during incubation of nickel disulfide in rat serum and renal cytosol precluded measurements of its dissolution half-times.

[f] Not determined.

Source: Sunderman (1984a).

TABLE 8-27. SUMMARY OF SURVIVAL DATA AND SARCOMA INCIDENCES IN CARCINOGENESIS TESTS BY INTRAMUSCULAR INJECTIONS OF 18 NICKEL COMPOUNDS

Category	Test Substance	Survivors at two years/ total no. of rats		Rats with local sarcomas/ total no. of rats		Median tumor latency (weeks)	Median survival period (weeks)	Rats with metastases/ rats with sarcomas	
Controls	Glycerol vehicle	25/40	(63%)	0/40	(0%)	-	>100	-	
	Penicillin vehicle	24/44	(55%)	0/44	(0%)	-	>100	-	
	All controls	49/84	(58%)	0/84	(0%)	-	>100	-	
Class A	Nickel subsulfide (αNi_3S_2)	$0/9^c$	(0%)	$9/9^c$	(100%)	30	39^b	5/9	(56%)
	Nickel monosulfide (βNiS)	$0/14^c$	(0%)	$14/14^c$	(100%)	40	48^b	10/14	(71%)
	Nickel ferrosulfide (Ni_4FeS_4)	$0/15^c$	(0%)	$15/15^c$	(100%)	16	32^b	10/15	(67%)
Class B	Nickel oxide (NiO)	$0/15^c$	(0%)	$14/15^c$	(93%)	49	58^b	4/14	(29%)
	Nickel subselenide (Ni_3Se_2)	$0/23^c$	(0%)	$21/23^c$	(91%)	28	38^b	18/21	(86%)
	Nickel sulfarsenide (NiAsS)	$0/16^c$	(0%)	$14/16^c$	(88%)	40	57^b	10/14	(71%)
	Nickel disulfide (NiS_2)	$0/14^c$	(0%)	$12/14^c$	(86%)	36	47^b	6/12	(50%)
	Nickel subarsenide (Ni_5As_2)	$0/20^c$	(0%	$17/20^c$	(85%)	22	44^b	9/17	(53%)
Class C	Nickel dust	$4/20^b$	(20%)	$13/20^c$	(65%)	34	42^b	6/13	(40%)
	Nickel antimonide (NiSb)	$9/29^b$	(31%)	$17/29^c$	(59%)	20	66^b	10/17	(59%)
	Nickel telluride (NiTe)	12/26	(46%)	$14/26^c$	(54%)	17	80^b	8/14	(57%)
	Nickel monoselenide (NiSe)	7/16	(44%)	$8/16^c$	(50%)	56	72^b	3/8	(38%)
	Nickel subarsenide ($Ni_{11}AS_8$)	$5/16^a$	(31%)	$8/16^c$	(50%)	33	88^b	6/8	(75%)
Class D	Amorphous nickel monosulfide (NiS)	$5/25^b$	(20%)	$3/25^b$	(12%)	41	71^b	3/3	(100%)
	Nickel chromate ($NiCrO_4$)	10/16	(63%)	1/16	(6%)	72	>100	1/1	(100%)
Class E	Nickel monoarsenide (NiAs)	13/20	(65%)	0/20	(0%)	-	>100	-	
	Nickel titanate ($NiTiO_3$)	11/20	(55%)	0/20	(0%)	-	>100	-	
	Ferronickel alloy ($NiFe_{1.6}$)	11/16	(75%)	0/20	(0%)	-	>100	-	

[a] $p < 0.05$ versus corresponding vehicle controls.

[b] $p < 0.01$ versus corresponding vehicle controls.

[c] $p < 0.001$ versus corresponding vehicle controls.

Source: Sunderman (1984a).

enter the cells as either phagocytized nickel particles or in a solubilized form. In contrast, the other two nickel compounds were actively taken up. Experiments with CHO cells suggest that at least 20 percent of the nickel measured in nuclei isolated from cells treated with nickel subsulfide is no longer part of a sedimentable particle with the same particle size and solubility properties as the parent compound. A substantial portion of the nickel associated with the nuclear fraction co-precipitates with the trichloroacetic acid insoluble fraction, which suggests that nickel strongly binds to cellular macromolecules. Costa et al. (1981b) found that particulate nickel compounds isolated from CHO cells after phagocytosis were more cytotoxic and induced more morphological transformations in SHE cells than did the same particulate compounds which had not been phagocytized.

8.2.3.3 Erythrocytosis Induced by Nickel Compounds. Sunderman et al. (1984) studied the association of erythrocytosis to renal cancers in rats exposed to 17 nickel compounds. Erythrocytosis (defined as peak hematocrit values that averaged >55 percent) occurred in 9 of 17 nickel-treated groups (NiS_2, β-NiS, α-Ni_3S_2, Ni_4FeS_4, NiSe, Ni_3Se_2, NiAsS, NiO, Ni dust). Renal cancers developed in 9 of 17 nickel-treated groups (NiS_2, β-NiS, α-Ni_3S_2, Ni_4FeS_4, NiSe, Ni_3Se_2, NiAsS, NiAs, NiFe alloy) within 2 years after the injections. The results of their studies are presented in Table 8-28. Using these results the authors concluded that rank correlation ($p < 0.001$) was observed between the incidences of erythrocytosis and renal cancers in the 17 nickel-treated groups. Rank correlation ($p < 0.001$) was observed between the present incidences of renal cancers and the sarcoma incidences previously reported following intramuscular administration of the 17 nickel compounds to Fischer 344 rats (14 mg Ni/rat). The incidences of renal cancer were not correlated with (1) the mass-fractions of nickel in the 17 compounds, (2) the dissolution half-times of the compounds in rat serum or renal cytosol, or (3) the phagocytic indices of the compounds in rat peritoneal macrophages.

Pronounced erythrocytosis and reticulocytosis and expanded blood volume occur in rats one to five months after intrarenal administration of nickel subsulfide (Hopfer et al., 1978; Jasmin and Riopelle, 1976; Morse et al., 1977). Erythrocytosis induced by intrarenal injection of nickel subsulfide is apparently due to enhanced production of renal erythropoietin (Hopfer et al., 1978; Solymoss and Jasmin, 1978). Jasmin and Solymoss (1975) reported that a single intrarenal injection of 10 mg of nickel subsulfide in rats induced pronounced

TABLE 8-28. CANCERS IN THE INJECTED KIDNEY OF RATS FOLLOWING INTRARENAL INJECTION OF NICKEL COMPOUNDS

Group	Treatment	No. of rats with renal cancer/total no. of rats	Peak hematocrit (%) in tumor-bearing rats[a]	Tumor latent period (weeks)	Rats with metastic renal cancer[b]	Histological types of renal cancers
A	Controls (saline)	0/46				
B	Controls (glycerol)	0/33				
C	Controls (Fe dust)	0/18				
D	Ni dust	0/18				
E	NiO	0/12				
F	NiS_2	2/10[c]	77-78	69-76	1	fibrosarcoma (2)
G	βNiS (cryst.)	8/14[d]	70-83	36-73	4	fibrosarcoma (3), mesangial cell sarcoma, leiomyosarcoma, rhabdomyosarcoma, renal cell carcinoma, carcinosarcoma
H	NiS (amorph.)	0/15				
I	αNi_3S_2	4/15[d]	76-82	35-61	4	mesangial cell sarcoma (4)
J	NiSe	1/12	80	46	1	fibrosarcoma
K	Ni_3Se_2	2/23	65-79	48-100	2	fibrosarcoma (2)
L	NiTe	0/19				
M	NiAsS	3/15[c]	61-66	44-73	3	carcinosarcoma, leiomyosarcoma, undifferentiated sarcoma
N	NiAs	1/20	56	95	0	renal cell carcinoma
O	$Ni_{11}As_8$	0/15				
P	Ni_5As_2	0/17				
Q	NiSb	0/20				
R	Ni_4FeS_4	1/12	78	36	1	undifferentiated sarcoma
S	$NiFe_{1.6}$(alloy)	1/14	51	25	0	nephroblastoma
T	$NiTiO_3$	0/19				

[a] Peak hematocrit values >55% were observed during 1-4 months post-injection in 22 of 23 rats that subsequently developed cancer in the injected kidney; peak hematocrit values averaged 73 ± 8% in rats with renal cancer.

[b] The most frequent sites of metastases were lung, peritoneum, liver, and spleen.

[c] $p < 0.05$ versus corresponding vehicle controls (Group A or B), computed by Fisher's Exact Test.

[d] $p < 0.001$ versus corresponding vehicle controls (Group A or B), computed by Fischer's Exact Test.

Source: Sunderman et al. (1984).

erythrocytosis. They observed a 1.5-fold increase in blood erythrocyte count and a 2.4-fold increase in erythrocyte mass 5 months following administration. Nickel subsulfide-induced erythrocytosis was not accompanied by alteration of erythrocyte 2,3-diphosphoglycerate levels. Jasmin and Solymoss (1975) speculated that erythrocytosis may have been mediated by increased erythropoietin levels. Oskarsson et al. (1981) evaluated the effects of nickel chloride and nickel subsulfide on the development of erythropoiesis in female Fischer 344 rats. Nickel chloride was administered by a single intrarenal injection. Nickel subsulfide was administered by continuous intraperitoneal infusion from an implanted osmotic minipump. Infusion of nickel chloride (0.85 mg Ni per day for 24 days) had no effect on blood hematocrit or reticulocyte counts. In contrast, a single intrarenal injection of nickel subsulfide caused pronounced erythrocytosis and reticulocytosis.

Jasmin and Riopelle (1976) studied the relationship between carcinogenicity and erythrocytosis in female Sprague-Dawley rats following administration of nickel and several other metal compounds. When nickel subsulfide was administered intravenously, no polycythemia or renal neoplasms were observed. Intrarenal administration of nickel subsulfide, in either glycerin or saline, rapidly caused erythrocytosis. Hemoglobin and erythrocyte values were significantly increased in the rats receiving nickel subsulfide intrarenally. Renal carcinomas were observed in approximately 40 percent of the treated animals. In general, erythrocytosis subsided approximately eight months after intrarenal injection of nickel subsulfide, even in those rats with renal carcinomas. Other nickel salts and a variety of other divalent metals failed to produce similar responses when administered by the intrarenal route.

Morse et al. (1977) found that the duration and magnitude of erythrocytosis induced by nickel subsulfide was dose-related. Female Fischer rats received single intrarenal injections of nickel subsulfide at dosages ranging from 0.6 to 10 mg per rat. Administration of nickel subsulfide induced marked erythrocytosis at all dose levels tested. The duration and magnitude of erythrocytosis was dose-related. Maximum erythrocytosis was observed approximately two months after intrarenal administration. This study also demonstrated that intramuscular injection of nickel subsulfide did not cause erythrocytosis at a dose of 10 mg/rat. The failure of erythrocytosis to develop after intramuscular injection is consistent with kinetic studies which show that after intramuscular injection of $^{63}Ni_3S_2$ in rats, ^{63}Ni II is slowly mobilized from the site of injection and excreted in the urine (Sunderman et al., 1976).

Gitlitz et al. (1975) found that proteinuria was induced in female Fischer rats after a single intraperitoneal injection of nickel chloride in dosages of 2 to 5 mg/kg. Generalized α-aminoaciduria was found after a single intraperitoneal injection of 4 to 5 mg/kg of nickel chloride. Amino acids in the plasma were normal or slightly diminished from 1 to 48 hours after administration of nickel II. Electron microscopy of kidneys of five rats sacrificed 48 hours after receiving 68 µmol/kg of nickel II revealed fusion of foot processes of glomerular epithelial cells. Focal tubular necrosis was present in the kidney of one of the rats examined. The proteinuria was probably due to glomerular injury. Aminoaciduria may have been due to inhibition of amino acid transport systems located in the luminal and/or peritubular membranes of the renal tubules and increased excretion of nickel-histidine chelate, one of several ultrafilterable complexes involved in the renal excretion of nickel II.

8.2.3.4 Interaction of Nickel Compounds with DNA and Other Macromolecules.

There is little information on the mechanism of nickel interaction with cellular nucleic acids. Recent studies have shown that nickel can cause DNA-protein crosslinks and DNA strand breaks. The work of Sirover and Loeb (1976) showed that metals can cause a decrease in the fidelity of DNA transcription. Robison et al. (1982) showed that nickel chloride and crystalline nickel monosulfide produce DNA strand breaks in CHO cells, while amorphous nickel monosulfide has no effect on DNA. Exposure to activated charcoal, which was actively phagocytized, had no effect on the DNA of CHO cells. The effect of nickel chloride and crystalline nickel monosulfide was both time- and concentration-dependent. Robison and Costa (1982) found that both nickel chloride and crystalline nickel monosulfide induced strand breaks in the DNA of CHO cells at concentrations which did not significantly impair normal cellular division. Crystalline nickel subsulfide, nickel chloride, and nickel monosulfide have been shown to induce concentration-dependent DNA repair in CHO cells (Robison et al., 1983). In contrast, amorphous nickel monosulfide did not induce DNA repair under similar experimental conditions.

Nishimura and Umeda (1979) studied the effects of nickel chloride, nickel acetate, potassium cyanonickelate, and nickel sulfide in a line of C3H mouse mammary carcinoma cells. All four compounds were readily taken up by the cells and reacted with protein, RNA, and possibly DNA. Measurements of leucine, uridine, and thymidine uptake during exposure showed that the synthesis of protein and DNA was more extensive than that of RNA. Nickel chloride, nickel acetate, nickel sulfide, and potassium cyanonickelate induced chromosomal aberrations consisting of gaps, breaks, and exchanges. Ciccarelli et al. (1981) observed dose-dependent lesions in DNA isolated from kidney nuclei obtained from rats 20 hours after intraperitoneal injection of nickel carbonate. DNA strand breaks and DNA-protein crosslinks were observed. Ciccarelli and Wetterhahn (1982) observed single strand breaks in lung and kidney nuclei and both DNA-protein and DNA interstrand crosslinks in kidney nuclei isolated from rat tissues following intraperitoneal injection of nickel carbonate.

A correlation was observed between tissue and intracellular nickel concentrations measured by electrothermal atomic absorption spectroscopy and the level of DNA damage and repair. Nickel carbonate had no effect on DNA isolated from the nuclei of liver or thymus. The ability of nickel to interact with cellular macromolecules and its demonstrated organotropic effects on DNA _in vivo_ may be related to its carcinogenic effects. Nickel II may be directly responsible for the DNA-protein crosslinks because in aqueous solution, nickel II is multifunctional, forming octahedral complexes (Cotton and Wilkinson, 1980). Nickel sulfide caused spindle fiber abnormalities in cultured rat embryo muscle cells (Swierenga and Basrur, 1968), and cylindrical laminated bodies in the contractile proteins of rabbit rhabdomyosarcomas (Hildebrand and Biserte, 1979b).

Many studies have shown that nickel II is capable of binding to protein as well as DNA. The formation of soluble complexes between nickel II, serum albumin, and serum ultrafiltrates has been observed in rats administered nickel chloride (Decsy and Sunderman, 1974; Van Soestbergen and Sunderman, 1972; Asato et al., 1975). Purified serum albumins from rabbits, rats, and man have been found to bind nickel II (Callan and Sunderman, 1973). Rao (1962) reported a strong interaction between nickel II and the imidazole groups of bovine serum albumin histidine residues, and a weak interaction with carboxylate groups. Tsangaris et al. (1969) found a strong interaction between nickel II and the amino-terminal residues and imidazole groups of histidine residues, and a weak interaction between nickel II and the sulfhydryl groups of cysteine residues. Lee et al. (1982) reported that solubilized nickel II is bound to DNA with an apparent equilibrium constant of 730 M^{-1} and with a saturation binding value of 1 nickel per 2.4 nucleotides. Spectroscopic and equilibrium binding studies of the interaction of nickel with DNA are consistent with the binding of nickel II to phosphate groups. DNA melting temperature studies performed by Eichhorn and Shin (1968) have shown that nickel II binds to both phosphate and base groups of DNA. However, nickel II has a much stronger affinity for DNA phosphate groups. X-ray crystallographic studies of the complexes between nickel II and unhindered nucleotides, inosine-5'-phosphate, guanosine-5'-phosphate, and adenosine-5'-phosphate showed that nickel II is bound directly to the N-7 position on the base and indirectly to two phosphate oxygen atoms through hydrogen-bonding of nickel-liganded water molecules (Clark and Orbell, 1974; DeMeester et al., 1974; Collins et al., 1975).

8.2.3.5 Induction of Morphological Transformation of Mammalian Cells in Culture. Casto et al. (1979a) demonstrated that nickel sulfate enhanced SA7 viral transformation of Syrian hamster embryo cells. Treatment with crystalline nickel subsulfide and nickel sulfate by DiPaolo and Casto (1979) resulted in the morphological transformation of Syrian hamster embryo (SHE) cells in a dose-related fashion, while amorphous nickel sulfide caused no transformations. Costa et al. (1982, 1981a,b, 1979) and Costa and Mollenhauer (1980a,b) studied the morphological transformations of mammalian cells in culture by several nickel compounds. Their studies have demonstrated that nickel compounds vary widely in their ability to induce morphological transformations of SHE cells. Costa and Mollenhauer (1980a,b) hypothesized that *in vitro* transformation ability of insoluble particulate nickel compounds are determined by their potential to be endocytosed. The data supporting the above reasoning have been summarized by Costa and Heck (1982) and Heck and Costa (1982), and are presented in Table 8-29.

Hansen and Stern (1983) compared the transformation activities of five nickel compounds (nickel welding fume, nickel subsulfide, nickel (III) oxide, nickel oxide, and nickel acetate) using baby hamster kidney (BHK-21) cells. They found that at 50 percent cell survival, the compounds produced equal numbers of transformed colonies. The authors postulated that the cell toxicity, and thus transforming activity of nickel compounds, depended on intracellular bioavailability of nickel II. They concluded that it takes ten times as much nickel oxide as nickel subsulfide to induce the same degree of transformation of BHK-21 cells.

Synergistic effects of nickel compounds with benzopyrene (BP) were observed by Costa and Mollenhauer (1980b) and Rivedal and Sanner (1981). The combined treatment of nickel sulfate and benzopyrene in Rivedal and Sanner's

TABLE 8-29. RELATIONSHIP BETWEEN PHAGOCYTOSIS AND INDUCTION OF MORPHOLOGICAL TRANSFORMATION BY SPECIFIC METAL COMPOUNDS

Metal compound (<5 μm particle size)	Phagocytosis activity[a]	Incidence of transformation[b] (percent relative to crystalline NiS)
Crystalline NiS	24%[c]	100%[c]
Crystalline Ni_3S_2	22%[c]	118%[c]
Crystalline Ni_3Se_2	27%[c]	115%
Amorphous NiS	3%	8%
Metallic Ni	4%	18%
Ni_2O_3	5%	17%
NiO	2%	9%
$NiCl_2$	ND	41%
Latex beads	ND	8%

[a] Determined in cultured Chinese hamster ovary cells [10 μg ml^{-1} exposure (1.27 μg cm^{-2}), 24 h]. Number of cells with metal particles/total number of cells examined.

[b] Number of transformed colonies/total number of surviving colonies.

Standardized to the incidence of transformation produced by crystalline NiS. (10 μg ml^{-1} exposure, 4 days).

[c] p <0.01 vs. amorphous metal sulfide X^2 test. ND, not determined.

Source: Costa and Heck (1982).

(1981) study showed a transformation frequency of 10.7 percent, as compared to 0.5 and 0.6 percent for nickel sulfate and benzopyrene alone. The cell transformations studied have been summarized by Sunderman (1984c), and the results are presented in Table 8-30.

8.2.3.6 Relative Carcinogenic Activity. Sunderman and Hopfer (1983) reported a significant rank correlation between the induction of erythropoiesis and carcinogenicity following the administration of particulate nickel compounds to rats at equivalent doses. The rank correlation suggests that certain nickel compounds produce both erythrocytosis and carcinogenesis in rats (Sunderman and Hopfer, 1983). These data do not provide a sufficient basis to conclude that the two phenomena are related biologically. However, pharmacokinetic data and studies showing that nickel subsulfide-induced erythrocytosis and carcinogenesis are both inhibited by manganese dust (Hopfer and Sunderman, 1978; Sunderman et al., 1979a, 1976) provide indirect evidence that these effects are related. Dissolution half-times and indices of phagocytosis, summarized in Table 8-26,

TABLE 8-30. MAMMALIAN CELL TRANSFORMATION BY NICKEL

Authors	Cells	Results
DiPaolo and Casto (1979)	SHE cells	$NiSO_4$, Ni_3S_2 pos.; amorph. NiS neg.
Costa et al. (1979, 1978)	SHE cells	Ni_3S_2 pos.; amorph. NiS neg.; transformed cells induce sarcomas in nude mice
Costa and Mollenhauer (1980a,b)	SHE cells	Transforming activity of cryst. Ni compounds related to phagocytosis rate
Costa et al. (1982)	SHE cells	Cryst. NiS potency 2.5-times that of $NiCl_2$
Saxholm et al. (1981)	C3H/10T 1/2 cells	Ni_3S_2 pos.; long microvilli in transformed cells
Hansen and Stern (1983)	BHK-21 cells	Ni dust, Ni_3S_2, Ni_2O_3, NiO and Ni acetate produce equal transformation percentages at equitoxic dosages
Rivedal and Sanner (1981)	SHE cells	Synergism between Ni II and benzo(a)-pyrene

Source: Sunderman (1984c).

have been proposed as indirect measures of carcinogenic potency of nickel compounds due to correlations observed between these variables and the incidence of injection site sarcomas. The results of Sunderman and Hopfer (1983) apparently contradict the hypothesis that the carcinogenic potency of particulate nickel compounds are related to dissolution rates or cellular uptake due to phagocytosis (Costa and Mollenhauer, 1980a,b). No significant rank correlations were observed between dissolution half-times or phagocytosis and the incidence of injection site sarcomas after administration of equipotent doses of nickel compounds by the intramuscular route. Until the mechanism of nickel carcinogenesis and associated processes are better understood, there is no *a priori* basis for using indices of phagocytosis, dissolution half-times, or erythrocytosis as predictors of the carcinogenic potency of particulate nickel compounds.

Sunderman (1984a) reported the incidence of injection site sarcomas in male Fischer rats administered nickel compounds by the intramuscular route.

Eighteen nickel compounds were tested at equivalent doses of 14 mg Ni/rat. Results from this study are presented in Table 8-27. The results of Sunderman (1984a) provide an adequate basis for ranking the relative carcinogenic activities of the compounds tested. Based on these data, the apparent relative carcinogenic activities of nickel compounds in decreasing order are Ni_3S_2 = βNiS cryst = Ni_4FeS_4 > NiO > Ni_3Se_2 > NiAsS > NiS_2 > Ni_5As_2 > Ni dust > NiSb > NiTe > NiSe = $Ni_{11}As_8$ > NiS amorphous > $NiCrO_4$. NiAs, $NiTiO_3$ and $NiFe_{1.6}$ were not carcinogenic under the conditions of this study. Based on the results of this study, the earlier observation of Gilman (1962) that nickel subsulfide is more active than nickel oxide in the induction of injection site sarcomas when injected intramuscularly, and the observation of Payne (1964) that nickel subsulfide is the most active among eight nickel compounds studied, with the following order of carcinogenic activities: Ni_3S_2 > $NiCO_3$ > NiO > $Ni(CH_3COO)_2$, it can be stated that nickel subsulfide is most active when administered intramuscularly.

In another series of studies, Sunderman et al. (1984) found that 9 of 17 nickel compounds tested carcinogenic when injected intrarenally at equivalent doses of 7 mg/rat. The results of the intrarenal injection study ranked the carcinogenic activities of nickel compounds by this route: βNiS crystalline > Ni_3S_2 > NiS_2 = NiAsS > Ni_3Se_2 = NiSe = $NiFeS_4$ > $NiFe_{1.6}$ > NiAs. It is apparent that the relative carcinogenic activities of different nickel compounds may be route-specific. Based upon the intrarenal studies, however, nickel subsulfide was still more active than other nickel compounds, with crystalline βNiS the most active.

To a more limited extent, Gilman's (1962) and Payne's (1964) observations on the relative carcinogenic activities of different nickel compounds support Sunderman's (1984a) data. Unquestionably, all three authors found nickel subsulfide to be the most potent of all nickel compounds studied by intramuscular injections.

8.2.4 Summary of Experimental Studies

Experimental nickel carcinogenesis test results and short-term *in vitro* test results that have evolved out of various laboratories are summarized in Table 8-31. Numerous investigators have reported tumors, particularly rhabdomyosarcomas and/or fibrosarcomas, following injection or implantation of nickel or its compounds. These investigations are summarized in Tables 8-14 through 8-24.

TABLE 8-31. SUMMARY OF ANIMAL AND IN VITRO TEST RESULTS OF SPECIFIC NICKEL COMPOUNDS

Nickel Compound (Number of studies)	Tumor Response, Route (Number of studies)	*In vitro* assays Response, test system
Ni_3S_2 (>40)	+ inhalation (1), heterotopic trachea (1) intramuscular injections and implants (>22) intrarenal injections (4) intratesticular injections (1) intraocular injections (2) subcutaneous injections (1) intrapleural (1)	+ cell transformation assay SHE and BHK-21 cell lines + sister chromatid exchange tests Inhibits DNA synthesis Nickel concentrates in cell nucleus Induces DNA strand breaks Induces DNA repair synthesis
	- buccal brushing (1) intrahepatic injections (2) submaxillary injections (1)	
Nickel metal powder (<20)	+ intramuscular injections (6) intrapleural " (2) intrafemoral " (2) intravenous " in rats (1)	+ cell transformation assay SHE cells (activity ~15% of Ni_3S_2) - sister chromatid exchange tests
	± inhalation (1), intrapulmonary (1)	
	- inhalation (4) intratracheal (1) intraperitoneal (1) intranasal (1) intrarenal (2) intravenous in mice and rabbits (1)	
NiO (>10)	+ intramuscular injections and implants (5) intrapleural injections (1)	+ cell transformation assays BHK-21 cell line (activity is ~1/10 of Ni_3S_2)
	± inhalation (1), intratracheal (1)	- cell transformation assays SHE cell line
	- inhalation (1) intratracheal injections (2) intrarenal (1)	
Ni_2O_3 (2)	± intracerebral injections	+ cell transformation assays SHE and BHK-21 cell lines (activity in SHE is ~1/10 of Ni_3S_2 and in BHK-21 $\simeq$ Ni_3S_2)
	- intramuscular injections	

(continued on following page)

TABLE 8-31. (continued)

Nickel Compound (Number of studies)	Tumor Response, Route (Number of studies)	*In vitro* assays Response, test system
Ni_2O_3 (2)	± intracerebral injections - intramuscular injections	+ cell transformation assays SHE and BHK-21 cell lines (activity in SHE is ~1/10 of Ni_3S_2 and in BHK-21 $\simeq$ Ni_3S_2)
$NiSO_4$ (5)	- intramuscular injections (4) ingestion (1)	+ cell transformation assay (activity ~½ of Ni_3S_2) + sister chromatid exchange tests + *in vitro* chromosomal aberration + gene mutation of yeast and mammalian cells in culture Induce B to Z conformational transition of DNA Decrease fidelity of DNA synthesis Enhancement of viral transformation
$NiCl_2$ (1)	- muscle implants	+ cell transformation assay (activity ~4/10 of Ni_3S_2) + sister chromatid exchange tests + *in vitro* chromosomal aberration + gene mutation of yeast and mammalian cells in culture + gene mutation in *S. typhimurium* 1A1535 and *Cornebacterium* Induce B to Z conformational transition of DNA Inhibit protein, RNA and DNA synthesis Induce DNA strandbreaks Induce DNA repair synthesis Inhibit interferon synthesis Decrease fidelity of DNA synthesis Ni bound to liver and kidney DNA

(continued on following page)

TABLE 8-31. (continued)

Nickel Compound (Number of studies)	Tumor Response, Route (Number of studies)	*In vitro* assays Response, test system
$NiCO_3$ (1)	+ muscle implant	Induce DNA-protein crosslink Induce DNA strandbreaks
$Ni(CH_3COO)_2$ (6)	+ intramuscular injections (2) intraperitoneal injections (2) - ingestion via drinking water (2)	+ cell transformation assay (activity ~1/10 of Ni_3S_2) Inhibit protein, RNA and DNA synthesis
$Ni(OH)_2$ (2) $Ni(OH)_2$ (1) colloidal	+ intramuscular injections - intramuscular injections	Not tested
Nickel refinery dusts (5)	+ intramuscular injections (1) intraperitoneal injections (1) ± inhalation (2) - inhalation (1)	Not tested
Nickelocene (2)	+ intramuscular injections	Not tested
$Ni(CO)_4$ (3)	+ inhalation (2) intravenous (1)	Ni bound to liver and kidney DNA Inhibit RNA polymerase
Ni_3S_2 + methylcholanthrene (1)	No effect, intramuscular injections shortened latency, intramuscular injections	
Ni_3S_2 + benzpyrene (2)	Doubled observed tumor rate, intratracheal injections	
Ni_3S_2 + manganese (2)	Inhibit tumor formation, intramuscular injections Inhibit tumor formation, intrarenal injections	
Ni_3S_2 + basic magnesium carbonate (1)	Inhibit tumor formation, intramuscular injections	

(continued on following page)

TABLE 8-31. (continued)

Nickel Compound (Number of studies)	Tumor Response, Route (Number of studies)	*In vitro* assays Response, test system
NiO + methylcholanthrene (1)	Cocarcinogenic, intratracheal injections	
NiO + smoke (1)	No effect, inhalation	
Ni + flyash (1)	No effect, inhalation	
Ni + methylcholanthrene (1)	Cocarcinogenic, intratracheal injections	
$NiSO_4$ + ethylnitrosourea (ENU)	Increase tumor obtained by ENU	
NiO + diethylnitrosourea (DENU)	Cocarcinogenic, intratracheal injections	
$NiSO_4$ + benzpyrene	Not studied	Increase cell transformation by 18 times Comutagenic

The significance of tumors resulting from the injection of chemicals has been the subject of considerable discussion. Most recently, Theiss (1982) pointed out that nearly half of the chemicals which induced local tumors only were not tumorigenic by other routes. This is certainly not the case with nickel subsulfide and nickel carbonyl, as they have produced tumors by inhalation.

Three studies of the carcinogenic potential of nickel salts in drinking water were found in the literature (Schroeder and Mitchener, 1975; Schroeder et al., 1974, 1964). All three studies produced negative results; however, all three used the same relatively low dose level of 5 ppm of nickel in the drinking water.

In the only ingestion study, Ambrose et al. (1976) administered nickel as sulfate hexahydrate fines ($NiSO_4 \cdot 6H_2O$; 22.3 percent nickel) in the diet of Wistar-derived rats and beagle dogs for two years. The dietary nickel concentrations were 100, 1000, and 2500 ppm. There were 25 rats and 3 dogs of each sex assigned to each dose group. A similar number of untreated animals were maintained and served as controls. No treatment-related tumors were observed from this study.

Sunderman et al. (1978) painted the buccal mucous membranes of Syrian golden hamsters with nickel subsulfide and observed no tumors.

Nickel carcinogenesis by inhalation has not been adequately studied. The Ottolenghi et al. (1974) study using nickel subsulfide and Fischer 344 rats is of adequate design to determine the carcinogenicity of nickel subsulfide by inhalation. The observed neoplasms were predominantly adenomas (8/110 male; 7/98 female) and adenocarcinomas (6/110 male; 4/98 female). Additional tumors were squamous cell carcinomas (2/110 male; 1/98 female) and a fibrosarcoma (one male). Inhalation studies using nickel carbonyl (Sunderman and Donnelly, 1965; Sunderman et al., 1959, 1957) have produced pulmonary tumors, although the studies have limitations due to high mortality from the high toxicity of nickel carbonyl.

Carcinogenesis testing of other nickel compounds by inhalation is either very limited or are nonexistent. In general, the results from animal inhalation studies for these compounds tend to be negative or equivocal. The National Toxicology Program is in the process of conducting inhalation carcinogenesis bioassays on nickel oxide, nickel sulfate, and nickel subsulfide. The studies on these compounds are in the subchronic dose-setting stage. The chronic inhalation studies will probably be complete by 1989. These studies, together with other biochemical and toxicological investigations of the scientific community, will provide a better database for the evaluation of the carcinogenicity of nickel compounds in the near future.

Nickel subsulfide (Ni_3S_2) is the most studied nickel compound. In a study of the carcinogenicities of various metal compounds, Gilman (1962) noted that nickel subsulfide was a potent inducer of rhabdomyosarcomas when given intramuscularly. Later studies of the carcinogenicity of nickel subsulfide demonstrated adenocarcinomas in rats given the substance intrarenally (Jasmin and Riopelle, 1976); rhabdomyosarcomas, fibrosarcomas, and fibrous histocytomas in rat testicular tissue after intratesticular dosing (Damjanov et al., 1978); and epidermoid and adenocarcinomas in the lung in Fischer 344 rats inhaling nickel subsulfide (Ottolenghi et al., 1974). Hamster fetal cells transformed by nickel subsulfide will induce sarcomas when injected subcutaneously into nude mice. In the study of Yarita and Nettesheim (1978), tracheas grafted onto isogenic rats showed mainly sarcomas but also a low yield of carcinomas with nickel subsulfide implantation as early as six months. Sunderman et al. (1980) extended the site tumorigenicity of nickel subsulfide to the eye, where injection of 0.5 mg into the vitreous cavity in rats led to a high incidence of ocular tumors by 8 months.

Differences in tumor response between species, strain, and route of administration, as well as dose-response relationships, have been observed. These observations have been well summarized by Sunderman (1983). The induction of morphological transformation of mammalian cells in culture and sister chromatid exchanges, the inhibition of DNA synthesis and induction of DNA strand breaks, and the observation of nickel concentrating in the cell nucleus are all supportive of the carcinogenicity of nickel subsulfide.

Nickel carbonyl administered to rats via inhalation produced pulmonary adenocarcinomas (Sunderman and Donnelly, 1965; Sunderman et al., 1959, 1957) and intravenous injections into rats produced malignant tumors at various sites (Lau et al., 1972). Biochemical studies have shown that the nickel from nickel carbonyl is bound to DNA and inhibits RNA polymerase activities.

Nickel containing dusts from refineries has been studied for potential carcinogenicity. Nickel refinery flue dust containing 68 percent nickel subsulfide, 20 percent nickel sulfate, and 6.3 percent nickel oxide produced either negative results (Kim et al., 1976; Belobragina and Saknyn, 1964) or equivocal results (Fisher et al., 1971) from inhalation studies. However, intramuscular injections produced strong tumor responses in rats and mice (Gilman and Ruckerbauer, 1962). The presence of squamous cell carcinomas in two of five surviving rats exposed to feinstein dust (Saknyn and Blohkin, 1978), an intermediate product of nickel refining containing nickel monosulfide, nickel oxide, and metallic nickel, lends credence to the concern that nickel refinery dusts are potential human carcinogens. These dusts have not been studied using in vitro short-term test systems or tests for macromolecular interactions.

Nickel metal, in the form of dust or pellets, has led to the induction of malignant sarcomas at the site of dosing in rats, guinea pigs, and rabbits (Heath and Webb, 1967; Heath and Daniel, 1964; Mitchell et al., 1960; Hueper, 1955), while inhalation of nickel dust has been reported to lead to lung anaplastic carcinomas and adenocarcinomas (Hueper, 1958). In the inhalation study of nickel dust carcinogenesis, Hueper (1958) reported that an alveolar anaplastic carcinoma was found in one guinea pig lung, and a "metastatic lesion" (lymph node) was found in a second animal. However, this study has been criticized as being inconclusive because the lymph node tumor could not be associated with a primary lung tumor, nor were control animals used in the guinea pig experiment.

Nickel oxide (NiO) produced sarcomas in five intramuscular injection studies (Sunderman, 1984a; Gilman, 1966, 1965, 1962; Payne, 1964) and one intrapleural injection study (Skaug et al., 1985). As in the case above, no controls were used in some of the intramuscular injection studies; however, in the intrapleural injection study, controls were used and the response by this route was strong, approaching that produced by nickel subsulfide. One inhalation study (Wehner et al., 1975) conducted on Syrian golden hamsters showed neither a carcinogenic effect of nickel oxide alone nor a cocarcinogenic effect with cigarette smoke. Another inhalation study (Horie et al., 1985) used too few animals to allow any definitive conclusions to be drawn. Responses from various intramuscular injection studies have varied depending on the dosage, animal species, and strain used. In general, where responses have been seen, nickel oxide has been shown to have a lower carcinogenic potential than nickel subsulfide. Cell transformation assays have given equivocal results: negative with SHE cells and positive with BHK-21 cells, with an activity about one-tenth that of nickel subsulfide.

Nickel (III) oxide (Ni_2O_3) has not been tested sufficiently to allow any conclusions to be drawn. Intracerebral injection (Sosinski, 1975) of nickel

(III) oxide produced a marginal tumor response in rats, but intramuscular injections did not. Furthermore, no tumors were produced in another intramuscular injection study (Payne, 1964). However, nickel (III) oxide has proven to be more active in the induction of morphological transformations of mammalian cells in culture than nickel oxide. The transforming activity in BHK-21 cells approximates that of nickel subsulfide, but in SHE cells it is only about one-tenth the activity of nickel subsulfide.

Soluble nickel compounds tested for carcinogenicity include nickel sulfate ($NiSO_4$), nickel chloride ($NiCl_2$), and nickel acetate ($Ni(CH_3COO)_2$). The results of four intramuscular injection studies (Kasprzak et al., 1983; Gilman, 1966, 1962; Payne, 1964) and one ingestion study (Ambrose et al., 1976) with nickel sulfate have been negative. Only one intramuscular implantation study (Payne, 1964), was conducted with nickel chloride, and the test results were negative. However, both the sulfate and the chloride induced morphological transformations of mammalian cells in culture; induced sister chromatid exchange, chromosomal aberrations *in vitro*, and gene mutations in yeast and mammalian cells in culture; decreased fidelity of DNA synthesis; and responded positively to other indicators of potential carcinogenicity. The observation (Stoner et al., 1976) of pulmonary tumors in strain A mice from the administration of nickel acetate by intraperitoneal injections, and the ability of nickel acetate to transform mammalian cells in culture to inhibit RNA and DNA synthesis, supports a concern that soluble nickel compounds may have carcinogenic potentials. However, tests on these soluble nickel compounds are too limited to support any definitive judgment.

The above discussion has focused on the ability of nickel compounds alone to induce carcinogenic responses. An equally important aspect of carcinogenicity is the interaction of nickel with other agents, since environmental situations entail simultaneous exposure to a number of such substances.

Experimental data exist to indicate that nickel has a cocarcinogenic or synergistic effect on the carcinogenicities of polycyclic aromatic hydrocarbons. Toda (1962) found that 17 percent of rats receiving intratracheal doses of both nickel oxide and 20-methylcholanthrene developed squamous cell carcinomas. Maenza et al. (1971) showed a synergistic rather than additive effect in the latency period reduction (30 percent) of sarcomas when simultaneous exposure to benzopyrene and nickel subsulfide was carried out. Kasprzak et al. (1973) observed pathological reactions in lungs of rats given both nickel subsulfide and benzopyrene that were greater than for either agent alone. However, Wehner et al. (1975) did not find a significant carcinogenic response of nickel oxide administered alone or with cigarette smoke. Syrian golden hamsters, whose sensitivity to inhaled particulate is questionable, were used.

Virus-nickel synergism is suggested by the observation of Treagan and Furst (1970) that *in vitro* suppression of mouse L-cell interferon synthesis occurs in response to the challenge of Newcastle Disease virus in the presence of nickel.

Nickel ion combined with benzo(a)pyrene enhanced the morphological transformation frequency in hamster embryo cells over that seen with either agent used alone (10.7 percent versus 0.5 percent and 0.6 percent for nickel and benzo(a)pyrene, respectively) at levels of 5 μg/ml nickel salt and 0.78 μg/ml benzo(a)pyrene. Furthermore, in a mutagenesis system using hamster embryo cells, as described by Barrett et al. (1978), a comutagenic effect between nickel sulfate and benzo(a)pyrene was also observed (Rivedal and Sanner, 1981, 1980). These observations are supported by cocarcinogenic effects between nickel compounds and certain organic carcinogens (Kasprzak et al., 1973; Maenza et al., 1971; Toda, 1962).

Comparative carcinogenicity of various nickel compounds has been studied and demonstrated in various laboratories (Sunderman et al., 1984, 1979b; Sunderman and Maenza, 1976; Jasmin and Riopelle, 1976; Payne, 1964; Gilman, 1962; Sunderman, 1984a).

Sunderman and Maenza (1976) studied the incidence of sarcomas in Fischer rats followed two years after single intramuscular injections of four insoluble nickel-containing powders: metallic nickel, nickel sulfide, α-nickel subsulfide, and nickel-iron sulfide matte. Amorphous nickel sulfide showed no tumorigenic potential, while nickel subsulfide was the most active of the test compounds. The relative carcinogenicity of nickel-iron sulfide matte was intermediate between nickel subsulfide and metallic nickel powder, suggesting to these authors that there may also be a previously unrecognized carcinogenic potential in other nickel-sulfur mineral systems, as well as the corresponding arsenides, selenides, and tellurides.

In a later study, Sunderman (1984a) reported the relative carcinogenic activities of 15 nickel compounds by administering equal dosages of compounds (14 mg Ni/rat) intramuscularly to rats. While nickel subsulfide was one of the most potent carcinogenic nickel compounds, crystalline nickel sulfide (NiS) was equally carcinogenic. Amorphous nickel sulfide was not carcinogenic under the conditions of this experiment.

Looking at the literature in aggregate, there appears to be a general inverse relationship between solubility and carcinogenic potential of the nickel compounds which have been studied--insoluble nickel metal, nickel oxide, and nickel subsulfide being variably carcinogenic, with most nickel salts generally being noncarcinogenic. It has been suggested that the prolonged contact of insoluble compounds is requisite to carcinogenic manifestation, the clearance of soluble nickel being shorter than the induction interval for such manifestation. However, careful examination of the data reveals that the mechanisms leading to carcinogenic manifestation may be more complex than basic postulates regarding the solubility or insolubility of nickel compounds.

Sunderman and Hopfer (1983) reported a significant rank correlation between the induction of erythropoiesis and carcinogenicity following the administration of particulate nickel compounds to rats at equivalent doses. Dissolution half-times and indices of phagocytosis, summarized in Table 8-26, have been proposed as indirect measures of carcinogenic potency of nickel compounds, due to correlations observed between these variables and the incidence of injection site sarcomas. The results of Sunderman and Hopfer (1983) contradict the hypothesis that the carcinogenic potency of a particulate nickel compound is related to dissolution rate or cellular uptake due to phagocytosis. No significant rank correlations were observed between dissolution half-times or phagocytosis and the incidence of injection site sarcomas after administration of equipotent doses of nickel compounds by the intramuscular route. Until the mechanism of nickel carcinogenesis and associated processes are more clearly understood, there is no _a priori_ basis for using indices of phagocytosis, dissolution half-times, or erythrocytosis as predictors of the carcinogenic potency of particulate nickel compounds.

A number of studies employing nickel compounds in various _in vivo_ and _in vitro_ test systems have been reported. These studies help to provide further insight on some of the mechanisms by which carcinogenic metals in general, and nickel in particular, may express such effects in intact organisms. Reviews by Sunderman (1984b,c, 1983, 1981, 1979) have summarized much of the pertinent literature.

Several authors have noted the enrichment of the nucleus with nickel when different nickel compounds are employed in various experimental systems. Webb and co-workers (1972) found that 70 to 90 percent of nickel in nickel-induced rhabdomyosarcomas was sequestered in the nucleus, of which half was in the nucleolus and half in nuclear sap and chromatin. In addition, nickel binding to RNA/DNA has been shown by both Beach and Sunderman (1970), using nickel carbonyl and rat hepatocytes, and Heath and Webb (1967), in nuclei from nickel subsulfide-induced rat rhabdomyosarcomas. In vivo inhibition of RNA synthesis by nickel compounds has also been demonstrated (Witschi, 1972; Beach and Sunderman, 1970).

The reports of Sirover and Loeb (1977) and Miyaki et al. (1977) demonstrate the ability of nickel ion (nickel sulfate) to increase the error rate (decreasing the fidelity) of DNA polymerase in E. coli and avian myeloblastosis virus.

Studies using test systems of varying complexity (Table 8-30) have demonstrated both the direct cellular neoplastic transformation potency of soluble nickel compounds (nickel sulfate, nickel choride), insoluble nickel compounds (Ni_3S_2, Ni_2O_3, NiO), and nickel dust, as well as the further enhancement of transformation due to viral inoculation (DiPaolo and Casto, 1979; Traul et al., 1979; Casto et al, 1979a,b; Costa et al., 1978). In one study, (Casto et al., 1979b) the nickel II enhancement of transformation in virally infected cells was seen to involve increased amounts of viral (SA7) DNA in cellular DNA, suggesting that enhancement of viral transformation results from damage to cell DNA, which then increases the loci for attachment of viral DNA.

In hamster cells in culture, nickel compounds have been shown to induce DNA strand breaks (Robison and Costa, 1982; Robison et al., 1982) and DNA repair synthesis (Robison et al., 1983). Recently, nickel has also been shown to form a protein-nickel-DNA complex in mammalian systems (Lee et al., 1982; Ciccarelli et al., 1981). These observations suggest that nickel compounds with carcinogenic activities can induce damage to DNA and form DNA-protein crosslinks.

While the mechanism of nickel carcinogenesis is not well understood, biochemical and macromolecular interaction studies and short term tests seem to indicate that the nickel ion may be the carcinogenic species. Thus, the difference in carcinogenic activities among different nickel compounds could be the result of the ability of the different nickel compounds to enter the cell and be converted to the nickel ion, and the chemical form and physical state of the nickel compounds are important determinants of their bioavailability.

8.3 QUANTITATIVE RISK ESTIMATION FOR NICKEL COMPOUNDS

8.3.1 Introduction

This quantitative section deals with the incremental unit risk for nickel in air and the potency of nickel relative to other carcinogens which the Carcinogen Assessment Group (CAG) of the U.S. Environmental Protection Agency has evaluated. The incremental unit risk estimate for an air pollutant is defined as the additional lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 mg/m^3 of the agent in the air they breathe. This calculation is done to estimate, in quantitative terms, the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: (1) to compare the carcinogenic potency of several agents with each other, and (2) to give a crude indication of the population risk that might be associated with exposures to air or water contaminated with these agents, if the actual exposures are known. The data used for the quantitative estimate is one or both of two types: (1) lifetime animal studies, and (2) human studies where excess cancer risk has been associated with exposure to the agent.

8.3.2 Quantitative Risk Estimates Based on Animal Data

8.3.2.1 Description of the Low-Dose Animal-to-Human Extrapolation Model. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, responses will also occur at all lower doses with an incidence determined by the extrapolation model. This is known as a nonthreshold model.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations which must be dealt with when evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly.

Based on observations from epidemiologic and animal cancer studies, and because most dose-response relationships have not been shown to be supralinear in the low dose range, the linear nonthreshold model has been adopted as the primary basis for animal-to-human risk extrapolation to low levels of the dose-response relationship. The risk estimates made with this model should be regarded as conservative, representing the most plausible upper limit for the risk, i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data. It is called a linearized model because it incorporates a procedure for estimating the largest possible linear slope (in the 95 percent confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\,[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where

$$q_i \geqq 0,\ i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp\,[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where

$$P_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d, or the effect of treatment.

The point estimate of the coefficients q_i, i = 0, 1, 2, ..., k, and consequently the extra risk function $P_t(d)$ at any given dose d, is calculated by maximizing the likelihood function of the data. (In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P).

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment including the control group. For nickel subsulfide, the only compound for which the data have been deemed suitable for animal-to-human dose-response extrapolation, the polynomial reduces to k = 1 or a one-hit model, since the only available inhalation study used one dose level plus a control.

The point estimate, q_1, and the 95 percent upper confidence limit of the extra risk $P_t(d)$ are calculated by using the computer program GLOBAL83, developed by Howe (1983, unpublished). At low doses, upper 95 percent confidence limits on the extra risk and lower 95 percent confidence limits on the dose producing a given risk are determined from a 95 percent upper confidence limit, q_1^*, on parameter q_1. Thus, the value q_1^* is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. It represents the 95 percent upper-limit incremental unit risk consistent with a linear nonthreshold dose-response model.

8.3.2.2 Selection of the Ottolenghi et al. (1974) Rat Inhalation Study. While the animal data base indicates that many nickel compounds induce cancer at the injection site, only nickel acetate and nickel carbonyl have been shown to cause tumors distal to the injection site. The one dietary and three low-level drinking water studies in which soluble nickel salts were given orally have shown no evidence of cancer.

Animal studies have shown sufficient evidence for carcinogenicity only for nickel subsulfide and nickel carbonyl. A risk estimate cannot be calculated from the nickel carbonyl inhalation experiment of Sunderman et al. (1959, 1975) because survival of the test animals was too poor. Only 9 of 96 (9 percent) of the exposed animals survived for 2 years. The toxicity can be attributed to the administration of nickel carbonyl in an alcohol-ether mixture, evidenced by the fact that only 3 of 41 (7 percent) of the vehicle control rats survived 2 years. In a subsequent experiment (Sunderman and Donnelly, 1965), only 1 of 64 rats chronically exposed to nickel carbonyl developed a lung tumor. In rats acutely exposed, two lung tumors were observed. Because the acute and chronically exposed groups cannot be combined, the number of lung tumors observed was too small for an incremental unit risk to be estimated from these data. A high incidence of malignant lymphomas was also observed in this experiment. The authors concluded that a relationship to nickel exposure appeared doubtful in view of a high spontaneous incidence of lymphoma in rats reported in the literature and found among control animals.

In the Ottolenghi et al. (1974) study, 110 male and 98 female Fischer 344 rats were exposed to 970 $\mu g/m^3$ nickel subsulfide via inhalation for 78 weeks (5 d/wk, 6 h/d). Compared with 108 male and 107 female controls, the treated groups of both sexes showed statistically significant increases in both adenomas and adenocarcinomas of the lung. These results have been shown in Table 8-13.

The results show signicant increases in adenomas and in combined adenomas/adenocarcinomas for both male and female rats and also an increased incidence of squamous cell carcinoma of the lung in treated males and females. Since the authors concluded that these "benign and malignant neoplasms...are but stages of development of a single proliferative lesion," a unit risk assessment can be calculated which includes combined adenomas and adenocarcinomas. This is also consistent with the Environmental Protection Agency's policy as stated in the Proposed Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 1984). Three other areas of concern with this study are: (1) the effects of the pretreatment injections of hexachlorotetrafluorobutane (HTFB) on lung tumors, (2) the low survival rates in the control groups, and (3) the differential survival between the control and nickel subsulfide-treated groups. Each of these factors must be either adjusted for or dismissed in carrying out the risk extrapolation procedure.

With respect to the issue of the effect of the injections of HTFB as a lung infarcting agent, the results showed that there were actually more infarcts in the controls (32 percent) than in the nickel subsulfide-treated rats (14 percent). However, no significant differences were seen in the injected versus the noninjected rats with respect to mortality, body weight gain, or lung tumor development. Of the rats receiving the injections, 15 percent had lung tumors compared with 13 percent of those not injected. Based on this analysis it is felt that no adjustment was needed for the injected animals.

With respect to the issue of low survival rates in the control groups, it is noted that only 31 percent of the controls survived until the end of the study. This compares with normal 104-week survival rates in the 50 to 60 percent range for many bioassays using the Fisher 344 rat. In comparing this difference, however, note must be taken that this bioassay actually lasted 114 weeks--4 weeks of subtreatment, followed by 78 to 80 weeks of exposure, and then 30 weeks of observation. Adjusting for the extra 10 weeks length in the appropriate chart in the Ottolenghi et al. (1974) paper shows that comparable 104-week control survival is actually in the 50 percent range. Therefore, it is felt that no adjustment is required for control survival.

Finally, with respect to the third issue of poor survival (5 percent) in the nickel-subsulfide treated groups, attention must be paid to the timing of this increased mortality and to the cause of death of the 29 nickel subsulfide-treated rats with lung tumors. Nearly all were observed toward the end of the exposure period or during the observation period. Ottolenghi and co-workers stated that the first observed adenocarcinoma occurred in a male rat dying in the 76th week of the experiment. Since at 76 weeks there had already been approximately 30 percent nontumor mortality in the nickel subsulfide-treated group (versus 20 percent in the controls, not statistically significant), the additional mortality due to tumors in the nickel subsulfide group was approximately 20 percent (29/145). Based on this analysis, nearly all of the difference in survival between the control animals (31 percent) and the treated animals (5 percent) can be explained by lung tumors. Therefore, no adjustment would be needed.

8.3.2.3 Calculation of Human Equivalent Dosages from Animal Data.

Two methods are presented for the human equivalent dosage based on the Ottolenghi et al. (1974) rat inhalation study. The first method (Section 8.3.2.3.1) assumes dose equivalence in units of mg/bw$^{2/3}$ for equal tumor response in the two species. The support for this method is that the ratios of lung mass to body weight are roughly equal in rat and man, that the lung is the only affected organ in rats, and that the general distribution, metabolism, and clearance of nickel subsulfide in the lung and cells is uncertain enough to be described in general terms. The equivalence of mg/bw$^{2/3}$ has been used in most of the Environmental Protection Agency's quantitative risk assessments.

The second method of calculating rat-to-human equivalence dose (Section 8.3.2.3.2) is based on mg/surface area of the lung dose equivalence between the two species. In this analysis adjustment is made for particle size, deposition (bronchiolar versus the alveolar regions), and clearance. As might be expected, attempts to model dose with increased detail can lead to more areas of uncertainty. Nevertheless, this analysis is included both as a comparison with the first method and as an attempt to further knowledge in the field.

8.3.2.3.1 Calculation of human equivalent dosages based on dose/body surface equivalence.

Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner. Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal

Then, the lifetime average exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

When exposure is via inhalation, agents that are in the form of particulate matter, such as nickel subsulfide, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, $v = mg/m^3$ of the agent in air, and r = the absorption fraction.

The inhalation rate, I, for rats can be calculated from the observations (Federation of American Societies for Experimental Biology, 1974) that rats weighing 113 g breathe 105 liters/day. For rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$I = 0.105\ (W/0.113)^{2/3}\ m^3/day$$

For the 300 g rats in the Ottolenghi et al. study, the daily inhaled amount of nickel subsulfide is as follows:

$$m = I \times 6/24 \times 970\ \mu g/m^3 = 48.8\ \mu g/day$$

For humans, the value of 20 m^3/day* is adopted as a standard breathing rate (International Commission on Radiological Protection, 1977).

The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previous stated relationships, are tabulated as follows:

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*From: Recommendation of the International Commission on Radiological Protection, page 9. The average breathing rate is 10 m^3 per 8-hour workday and 20 m^3 in 24 hours.

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.67

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species. This would be the case for nickel subsulfide. Thus, rearranging the above equation and solving for v_h gives

$$v_{humans} = (i_{rats}/i_{humans})\,(W_{rats}/W_{humans})^{1/3} v_{rats}$$

Filling in the numbers gives

$$v_h = (0.67/0.29)(0.30/70)^{1/3} \times 122.8\ \mu g/m^3 = 46.1\ \mu g/m^3$$

as the human equivalent continuous exposure, since the daily equivalent exposure in the Ottolenghi et al. study is

$$970\ \mu g/m^3 \times \frac{6}{24}\text{ hours} \times \frac{5}{7}\text{ days} \times \frac{78}{110}\text{ weeks} = 122.8\ \mu g/m^3$$

8.3.2.3.2 Dosimetric considerations. When extrapolating results from animal inhalation studies to humans several factors have to be considered:

1. The deposition of the inhaled chemical throughout the respiratory tract. Deposition in nasopharyngeal, tracheobronchial and alveolar regions should be separated. The deposition in these regions depends on respiratory

parameters (respiratory geometry, breathing volume and frequency) and particle parameters (aerodynamic size, hygroscopicity, and heterodispersity). However, not only is total regional deposition of importance but the dose deposited per unit surface area of a specific region should also be evaluated. Although this delivered dose may not be equivalent to the dose to a target site in the respiratory tract--clearance mechanisms having to be taken into account--it may give an indication of where possible effects can be expected to occur.

2. Retention half-time of the inhaled particles. This is dependent on many factors, e.g., solubilization in the lung, uptake by macrophages, and uptake into epithelial cells. Retention may also be affected by chronic exposure to the substance itself if this substance influences lung clearance. The *in vivo* solubility of different nickel compounds seems to differ considerably, with water soluble nickel salts being rapidly solubilized and nickel oxide being solubilized much more slowly in the lung (although still to a much higher degree than in water). Nickel subsulfide, also insoluble in water, seems to be solubilized in the lung to a higher extent than nickel oxide, as judged by its short pulmonary retention half-time of about 12 days in mice (Valentine and Fisher, 1984) and from nickel excretion rates in urine. Accumulation of nickel in the respiratory tract during chronic exposure conditions depends on all of these parameters.

3. Metabolism of the inhaled compound. After solubilization in the lung, possibly inside macrophages, the retention could be influenced by tissue binding in the lung and by elimination rates via feces and urine. While this may be different in humans and small laboratory animals for the same compound, it has yet to be determined for nickel.

4. Differences in sites of tumor induction. The sites of tumor induction may be different in man and animals, e.g., bronchogenic versus alveologenic tumors. Thus, the region of the target cells in the respiratory tract has to be considered when extrapolating from animal studies.

These four points will be discussed in the following section dealing with extrapolating results from the inhalation study by Ottolenghi et al. (1974). In this study, male and female Fischer 344 rats were exposed for 78 weeks to 970 μg Ni_3S_2/m^3, 6 hours/day, 5 days per week. From the sparse information on particle sizes given in the paper (70 percent of the mass smaller than 1 μm and 25 percent between 1 and 1.5 μm geometric diameter), the following particle parameters can be deduced, assuming that the particle size distribution was log-normal: the density, rho, of nickel subsulfide is 5.82 g/cm^3, i.e., a particle with geometric diameter, D_g, of 1 μ, would have an aerodynamic diameter, D_{ae}, of 2.41 μm ($D_{ae} = D_g \cdot$ rho). Under the above mentioned assumption of a log-normal distribution, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles used in the Ottolenghi et al. study were: MMAD = 2.0 μm, GSD = 1.47.

Under the exposure conditions of the study, both benign and malignant tumors of the respiratory tract developed to a significant degree in the animals. There was no clear distinction between tumors of bronchogenic and alveolar origin; tumors of both types were induced. Since nickel concentrations in the lungs were not reported, the question about the levels of nickel having accumulated in the lungs can only be approximated. In the following cases, respective calculations are performed assuming different respiratory tract retention behavior of the inhaled nickel subsulfide.

Case 1: The retention half-time of nickel subsulfide in the alveolar region is 12.4 days as determined for the mouse lung by Valentine and Fisher (1984) after a single intratracheal instillation. Bronchial clearance is assumed not to be disturbed and to occur with a retention half-time of 1.2 days (Valentine and Fisher, 1984). Nasopharyngeal clearance is also assumed to be undisturbed with a half-time of 0.5 days.

Case 2: The retention half-time is significantly longer, because the species is different (rat, Ottolenghi; mouse, Valentine and Fisher) and because a chronic continuous exposure to nickel subsulfide may lead to an impairment of alveolar clearance mechanisms for the compound. The latter is indicated in hamster studies by Wehner et al. (1981) who found that chronic exposure to fly ash with high nickel content considerably increased retention of nickel in the lung compared to fly ash with low nickel content. Oberdörster and Hochrainer (1980) also observed a decrease in alveolar particle clearance during continuous exposure to nickel oxide particles at a concentration of 50 μg/m^3 in the rat. Particle retention half-time was 520 days under these conditions, whereas a single exposure to nickel oxide resulted in a pulmonary retention half-time for nickel of 36 days (Hochrainer et al., 1980). This represents an almost 15-fold increase in retention half-time. Whether lung clearance of nickel oxide particles and other particles is affected in the same way by chronic nickel exposure has not been determined; however, the studies by Wehner et al. (1981) and Tanaka et al. (1985) support this assumption. Nickel subsulfide appears to have a more rapid *in vivo* solubility than nickel oxide (Kuehn and Sunderman, 1982). However, without experimental data it is impossible to determine whether under the chronic exposure conditions of the Ottolenghi et al. study, nickel subsulfide solubility would be different from nickel oxide. Thus, for this case, an increased pulmonary retention half-time of 500 days will be assumed. Bronchial clearance is also assumed to be affected due to development of bronchitis, the retention half-time increasing to 30 days. Nasal clearance is assumed to be affected, as demonstrated in humans (Torjussen and Andersen, 1979), and has a long half-time of 100 days.

Case 3: The assumption is made that nickel subsulfide is not cleared at all from the respiratory tract; hence, the total deposited dose is delivered to the respiratory tract.

Since no data for nickel clearance in the nasopharyngeal area in rodents are available, the retention data used for this region are only provided to illustrate the outcome under the assumed different retention characteristics.

The following calculations on respiratory tract deposition are derived by using a lung model described by Schum and Yeh (1980) and Yeh and Schum (1980). The deposition calculations are based on anatomical models reflecting the asymmetrical branching of the bronchial tree present in the mammalian lung. The model uses a typical path which particles follow when inhaled. Particle size and density and respiratory pattern (e.g., total lung capacity, functional residual capacity, tidal volume, and breathing rate) can be adjusted independently in the mathematical model to reflect realistic values. The dimensions for the anatomical model were determined from silicone rubber casts of the bronchial tree of rats and humans and include diameter, length, branching angles, and gravity angle of the airways. The model represents a system of cylindrical tubes connected in a typical branching pattern for each airway generation starting at the trachea (generation 1) to the acini (generation 17 to 25). Deposition of inhaled particles is assumed to occur by diffusion, sedimentation, and impaction during inhalation, and by diffusion and sedimentation during exhalation (Schum and Yeh, 1980; Yeh and Schum, 1980). As shown by the authors, predicted depositions from the model agree quite well with experimental studies in rats (Raabe et al., 1977) and humans (Lippmann, 1977).

The inhaled minute volume and respiratory frequency for the rats in the Ottolenghi et al. study are predicted according to Stahl (1967):

Minute Volume: $$V_M = bw^{0.8} \times 379 \text{ (ml)} \tag{1}$$

Respiratory Rate: $$F_R = bw^{-0.26} \times 53.5 \text{ (min}^{-1}\text{)} \tag{2}$$

Tidal Volume: $$V_T = V_M/F_R \tag{3}$$

As an approximation for mean body weight (bw, in kilograms) of the rats in the Ottolenghi et al. study, a value of 0.3 kg is assumed. This gives $V_M = 144.66$ ml, $F_R = 73.16\ \text{min}^{-1}$, and $V_T = 1.98$ ml.

The amount A_t of nickel accumulated at time t is determined by:

$$A_t = \frac{a}{b}(1 - e^{-bt}) \tag{4}$$

where a is the amount being deposited each day and b is the elimination rate

$$b = \frac{\ln 2}{T_{1/2}}$$

(Task Group on Metal Accumulation, 1973). For retention in the tracheobronchial tree, only the accumulation of the newly deposited nickel subsulfide particles is calculated. Nickel subsulfide particles cleared from the alveolar region and passed through the tracheobronchial region are not included; no data are available for this portion of nickel subsulfide.

Since the rats were only exposed for five days each week, a was adjusted to

$$a' = \frac{a \times 5}{7} \tag{5}$$

to account for the two days of no exposure. This changes the accumulation to:

$$A_t' = \frac{a'}{b} (1-e^{-bt}) \qquad (6)$$

The equilibrium or steady state value is given by

$$A_t' = \frac{a'}{b} \qquad (7)$$

In addition, the influence of heterodispersity is included in the following calculations and deposition both for a monodisperse nickel subsulfide aerosol and for one with a geometric standard deviation of 1.47 is calculated.

Since the geometric standard deviation of the nickel subsulfide particle size distribution of the Ottolenghi et al. study is rather low, the influence on regional deposition is expected to be small. This is shown in Table 8-32, where the percent predicted regional deposition according to the model by Schum and Yeh (1980) is given. With bigger geometric standard deviations, differences can become larger, in particular with regard to deposition within a given generation of the respiratory tract.

The amount, M, of nickel subsulfide inhaled daily by the rats in the Ottolenghi et al. study is given by:

$$M = V_M \times T \times C \times 10^{-6} \ (\mu g) \qquad (8)$$

TABLE 8-32. RELATIVE DEPOSITION OF MONODISPERSE AND HETERODISPERSE PARTICLES IN REGIONS OF THE RESPIRATORY TRACT OF RATS.[a]

Region	Monodisperse	Heterodisperse GSD = 1.47
Nasopharyngeal	16.14	22.69
Tracheobronchial	3.78	3.59
Pulmonary	6.02	5.54

[a] Values given are percent of inhaled particle mass deposited in respective regions. MMAD = 2.0 μm; GSD = 1.47

where T is the exposure time in minutes (360 min) and C is the exposure concentration in $\mu g/m^3$ (970 $\mu g/m^3$). This gives a daily inhaled amount of 50.5 µg, which compares with 48.8 µg in Section 8.3.2.3.1.

Based on the deposition data (Table 8-32) and on the amount of nickel subsulfide inhaled, the amount of nickel subsulfide deposited daily in these regions of the respiratory tract in the rat [a in equation (4)] is shown in Table 8-33. Also shown is the amount adjusted for seven days per week exposure (a').

TABLE 8-33. AMOUNT OF NICKEL SUBSULFIDE (µg) DEPOSITED DAILY IN REGIONS OF THE RESPIRATORY TRACT OF RATS

Region	Monodisperse		Heterodisperse GSD = 1.47	
	a	a'	a	a'
Nasopharyngeal	8.15	5.82	11.46	8.19
Tracheobronchial	1.91	1.36	1.81	1.29
Pulmonary	3.04	2.17	2.80	2.00

a = daily deposition during 5 day/week exposure; a' = daily deposition adjusted for 7 day/week exposure.

Calculation of nickel subsulfide accumulation in regions of the respiratory tract according to equation (6) after 78 weeks of exposure is exemplified for Case 1, monodisperse particles. (Calculations for Cases 2 and 3 were performed in the same way using the respective values, and all results are summarized in Table 8-34.)

Case 1: Pulmonary retention half-time, 12.4 days; bronchial retention half-time, 1.2 days; monodisperse particles:

a) Pulmonary region:

$$A'_{alv} = a'_{alv}/b_{alv}\ (1 - e^{-b_{alv}t}) \qquad (9)$$

$$(a'_{alv} = 2.17\ \mu g;\ b_{alv} = \frac{\ln 2}{12.4} = 0.0559;\ t = 546\ \text{days})$$

$$A'_{alv} = 38.8\ \mu g$$

TABLE 8-34. EQUILIBRIUM VALUES AND ACCUMULATION OF NICKEL SUBSULFIDE[a] IN THE NASOPHARYNGEAL (NP), TRACHEOBRONCHIAL (TB), AND PULMONARY (P) REGIONS OF RATS AFTER 78 WEEKS OF EXPOSURE AND ASSUMING THREE DIFFERENT RETENTION HALF-TIMES (MONODISPERSE PARTICLES)

		Retention $T_{1/2}$, days	Clearance rate, day^{-1} $\ln 2/T_{1/2}$	Accumulation at 78 weeks	Accumulation at equilibrium
NP	(1)[b]	0.5	1.3863	4.20	4.20
	(2)	100	0.0069	823.98	843.48
	(3)	infinite	0	3177.72	no eqilibr.
TB	(1)	1.2	0.5776	2.35	2.35
	(2)	30	0.0231	58.87	58.87
	(3)	infinite	0	742.56	no equilibr.
P	(1)	12.4	0.0559	38.82	38.82
	(2)	500	0.0014	828.30	1550.00
	(3)	infinite	0	1184.82	no equilibr.

[a] μg/region

[b] (1) = Case 1; (2) = Case 2; (3) = Case 3. See text.

MMAD = 2.0 μm.

Due to the short half-time, this is already the equilibrium value.

b) Tracheobronchial region:

$$A'_{tb} = a'_{tb}/b_{tb}\,(1 - e^{-b_{bt}t})$$

$$(a'_{tb} = 1.36\ \mu g;\ b_{tb} = \frac{\ln 2}{1.2} = 0.5776;\ t = 546\ \text{days})$$

$$A'_{tb} = 2.35\ \mu g$$

This is also the steady state value; however, as indicated before, it does not include nickel subsulfide cleared via the mucociliary escalator from the tracheobronchial tree.

Table 8-35 shows the amount of the accumulated nickel subsulfide after 78 weeks of exposure, as well as the equilibrium values, for heterodisperse

TABLE 8-35. EQUILIBRIUM VALUES AND ACCUMULATION OF NICKEL SUBSULFIDE[a] IN THE NASOPHARYNGEAL (NP), TRACHEOBRONCHIAL (TB), AND PULMONARY (P) REGIONS OF RATS AFTER 78 WEEKS OF EXPOSURE AND ASSUMING THREE DIFFERENT RETENTION HALF-TIMES (HETERODISPERSE PARTICLES)

		Retention $T_{1/2}$, days	Clearance rate, day^{-1} ln $2/T_{1/2}$	Accumulation at 78 weeks	Accumulation at equilibrium
NP	(1)[b]	0.5	1.3863	5.91	5.91
	(2)	100	0.0069	1159.52	1186.96
	(3)	infinite	0	4471.74	no eqilibr.
TB	(1)	1.2	0.5776	2.23	2.23
	(2)	30	0.0231	55.84	55.84
	(3)	infinite	0	704.34	no equilibr.
P	(1)	12.4	0.055	35.78	35.78
	(2)	500	0.0014	763.41	1428.57
	(3)	infinite	0	1092.00	no equilibr.

[a] μg/region

[b] (1) = Case 1; (2) = Case 2; (3) = Case 3. See text. MMAD = 2.0 μm; GSD = 1.47.

particles. Figures 8-1 through 8-3 depict accumulation behavior for the heterodisperse nickel subsulfide particles in the different regions of the respiratory tract, calculated for three different retention half-times. A steady state or equilibrium value is reached within the exposure period of 78 weeks in all cases except when the retention half-time is assumed to be 500 days (pulmonary region, Figure 8-3). In this case, the amount accumulated after 78 weeks of exposure is 764 μg, whereas the equilibrium value is 1429 μg.

Since none of the assumed retention half-times have been experimentally proven for nickel subsulfide, the tables and figures are not intended to give exact values for nickel accumulation in the respiratory tract, but mainly show the differences in accumulation of nickel for the different cases. Approximate equilibrium values are reached after about ten half-times.

In the study by Ottolenghi et al. (1974), tumors developed in both the bronchial and alveolar regions of the lung. The surface area of a respective lung region is conceivably an important factor for dosimetric considerations because the total dose deposited in a certain region is not equivalent to the

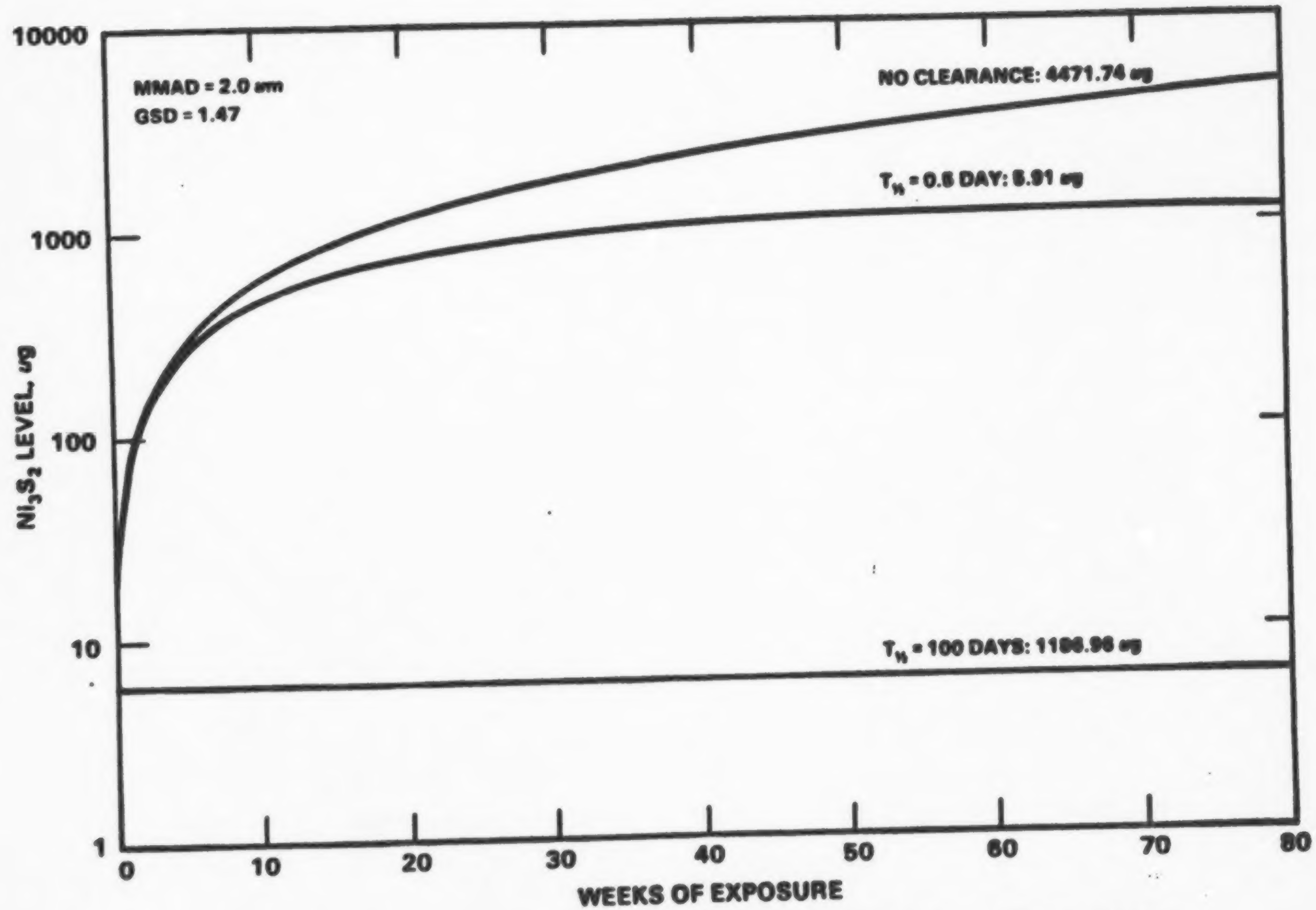

Figure 8-1. Accumulation of Ni_3S_2 in the nasopharyngeal region of the rat during chronic exposure of Ni_3S_2 for 78 weeks with daily deposition of 8.19 ug and different retention characteristics.

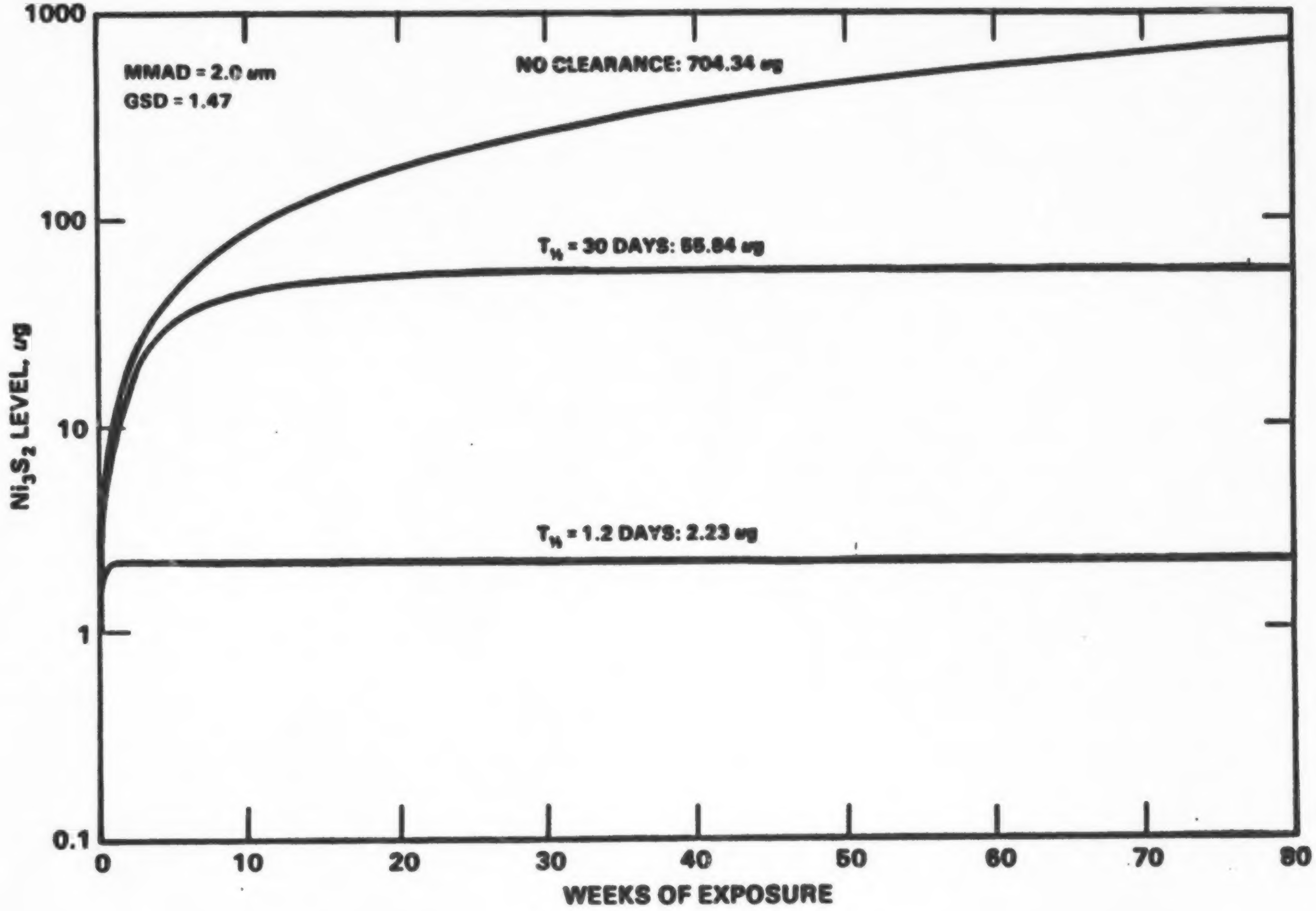

Figure 8-2. Accumulation of Ni_3S_2 in the tracheobronchial region of the rat during chronic exposure of Ni_3S_2 for 78 weeks with daily deposition of 1.29 ug and different retention characteristics.

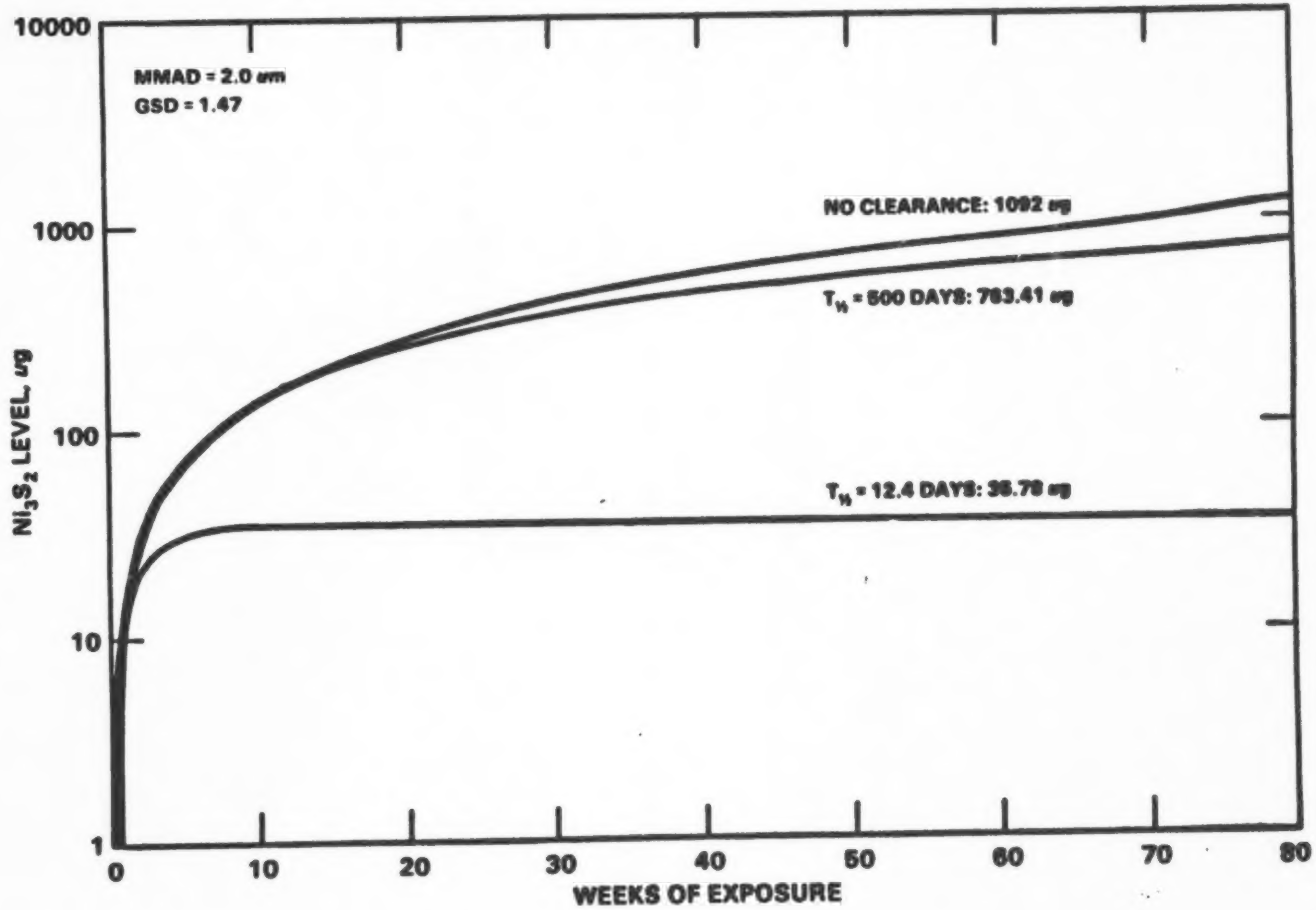

Figure 8-3. Accumulation of Ni_3S_2 in the pulmonary region of the rat during chronic exposure of Ni_3S_2 for 78 weeks with daily deposition of 2.0 ug and different retention characteristics.

dose per surface area. For example, although only 3 percent of inhaled nickel subsulfide may deposit in the tracheobronchial region and 6 percent in the alveolar region of the respiratory tract of the rat, the respective surface areas are about 40 cm^2 for the tracheobronchial region and about 4,000 cm^2 for the pulmonary region. Thus, although twice as much nickel subsulfide may have been deposited in the alveolar region than in the bronchial region, the surface area dose for the tracheobronchial region is about 50 times greater than for that of the pulmonary region. For humans, regional deposition differs from that in the rat and the surface area dose will also be different from the rat.

In the following section, lung surface areas of rat and man are compared, as well as the deposited surface area dose for the tracheobronchial region and for the pulmonary region under the exposure conditions of the Ottolenghi et al. study. In addition, the deposited surface area dose per airway generation in the two species is compared. Finally, the total dose per surface area of the human lung under these exposure conditions is calculated, both for discontinuous exposure (6 hrs/d, 5 d/wk), and for continuous exposure (24 hrs/d, 7 d/wk).

Lung surface area and deposited surface area dose are predicted using the anatomical dimensions for the airways given by Schum and Yeh (1980) and Yeh and Schum (1980). The following surface areas can be calculated for a 300 g rat with a tidal volume of 1.98 cm^3 and a normal man with a tidal volume of 750 m^3 (ICRP Task Group on Lung Dynamics, 1966):

Rat:	Tracheobronchial surface (cm^2):	45.7
	Pulmonary surface (cm^2):	4,453
Man:	Tracheobronchial surface (cm^2):	4,060
	Pulmonary surface (cm^2):	548,789

The predicted percent deposition of the inhaled particles for the rat is 3.59 percent for the tracheobronchial region and 5.54 percent for the pulmonary region (Table 8-32). For man, the respective percentages are 3.94 and 18.18 percent for particles with MMAD of 2.0 μm and GSD of 1.47.

With these data, the amount deposited during a 6-hour exposure to 970 $\mu g/m^3$ can be calculated (rat: tidal volume = 1.98 cm^3; respiratory frequency = 73 min^{-1}; man: tidal volume = 750 cm^3; respiratory frequency = 15 min^{-1}; amount of nickel subsulfide inhaled daily during 6 hours by human: 3928.5 μg). The daily deposited surface area dose of nickel subsulfide in rat and man, under the conditions of the Ottolenghi et al. study, are as follows:

Rat:	Tracheobronchial surface area dose (ng/cm^2):	39.52
	Pulmonary surface area dose (ng/cm^2):	0.63
Man:	Tracheobronchial surface area dose (ng/cm^2):	38.12
	Pulmonary surface area dose (ng/cm^2):	1.30

The tracheobronchial region receives an approximately 30-fold higher dose (man) and 60-fold higher dose (rat) per surface area than the pulmonary region. The amount deposited per cm^2 of tracheobronchial surface is essentially the same in both the rat and man, whereas deposited pulmonary surface area dose in man is twice that of the rat. However, since clearance mechanisms are effective in both regions, the deposited dose must be adjusted to reflect the accumulated long-term dose.

Before this long-term dose is calculated, differences in the deposited surface area dose per airway generation will briefly be compared between the two species. Figure 8-4 shows the predicted deposited nickel subsulfide per cm^2 of each airway generation in rat and man. Deposits onto airway generation areas 16 through 25 are considered to be in the pulmonary region. In general, specific surface area deposition is higher in both the proximal airway generations and in the pulmonary region in man than in the rat during the six-hour exposure. As noted above, clearance of nickel subsulfide over the six-hour exposure period will occur to a certain extent, particularly in the tracheobronchial region, but is not considered here.

The accumulated surface area dose in rat and man of nickel subsulfide under the conditions of the Ottolenghi et al. study is shown in Figure 8-5. Because of the lack of retention data for inhaled nickel subsulfide in either species, available retention half-times for nickel oxide in rats and for slightly soluble particles in humans were used. This assumes, however, that clearance mechanisms were not influenced by chronic exposure, an assumption which is probably not justified for low concentrations of environmental exposure. Thus, the tracheobronchial clearance rate is assumed to be 0.8664 ($T_{1/2}$ = 0.8 days) for rat and man, and pulmonary clearance is assumed to be 0.0193 ($T_{1/2}$ = 36 days) for the rat

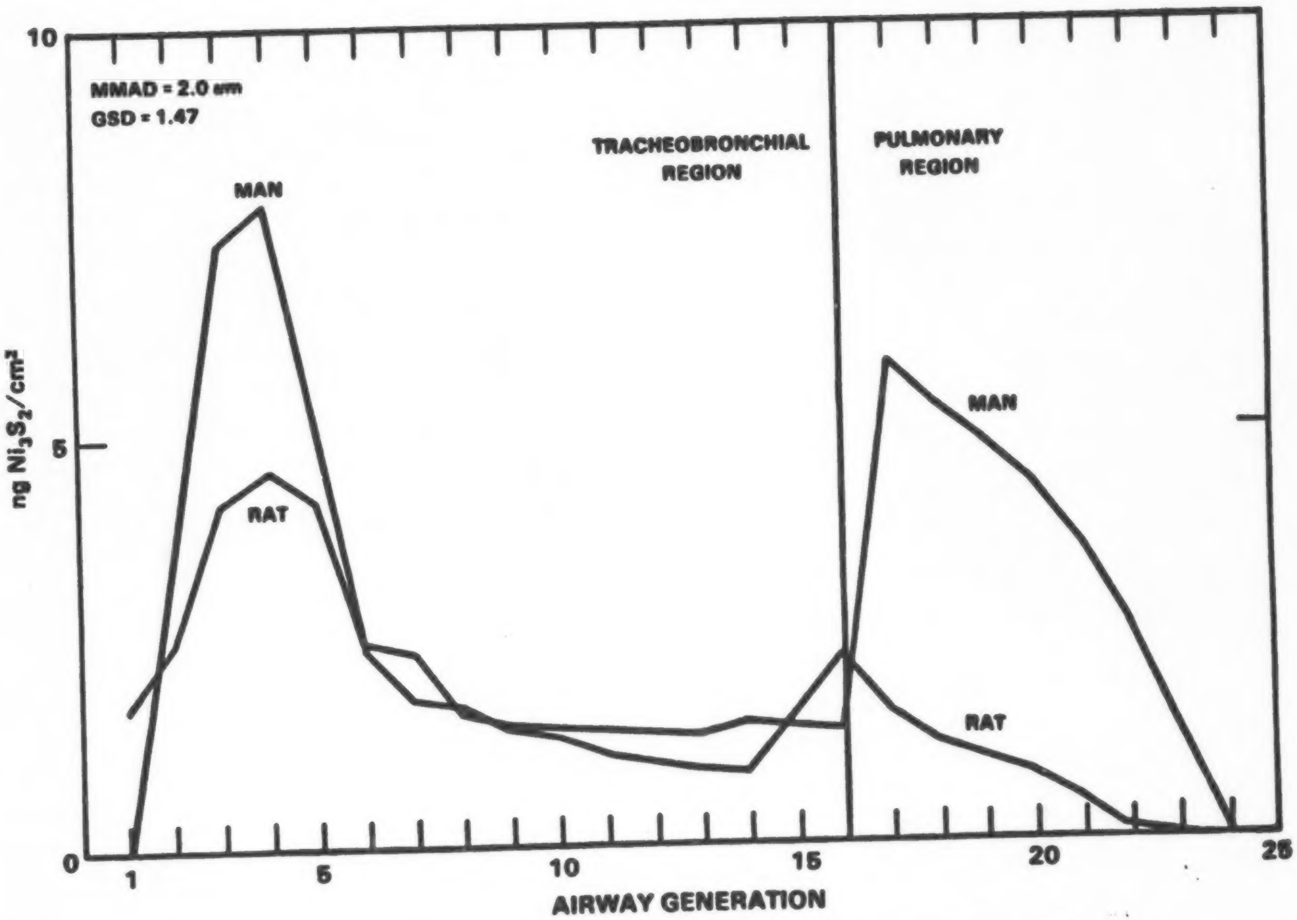

Figure 8-4. Predicted Ni_3S_2 particle deposition on surface area (assuming even distribution) per airway generation in rat and man after 6-hour exposure to 970 ug/m³. Trachea = generation 1; terminal bronchioles = generation 16; pulmonary region (respiratory bronchioles, alveolar ducts and alveoli): generations 17-25.

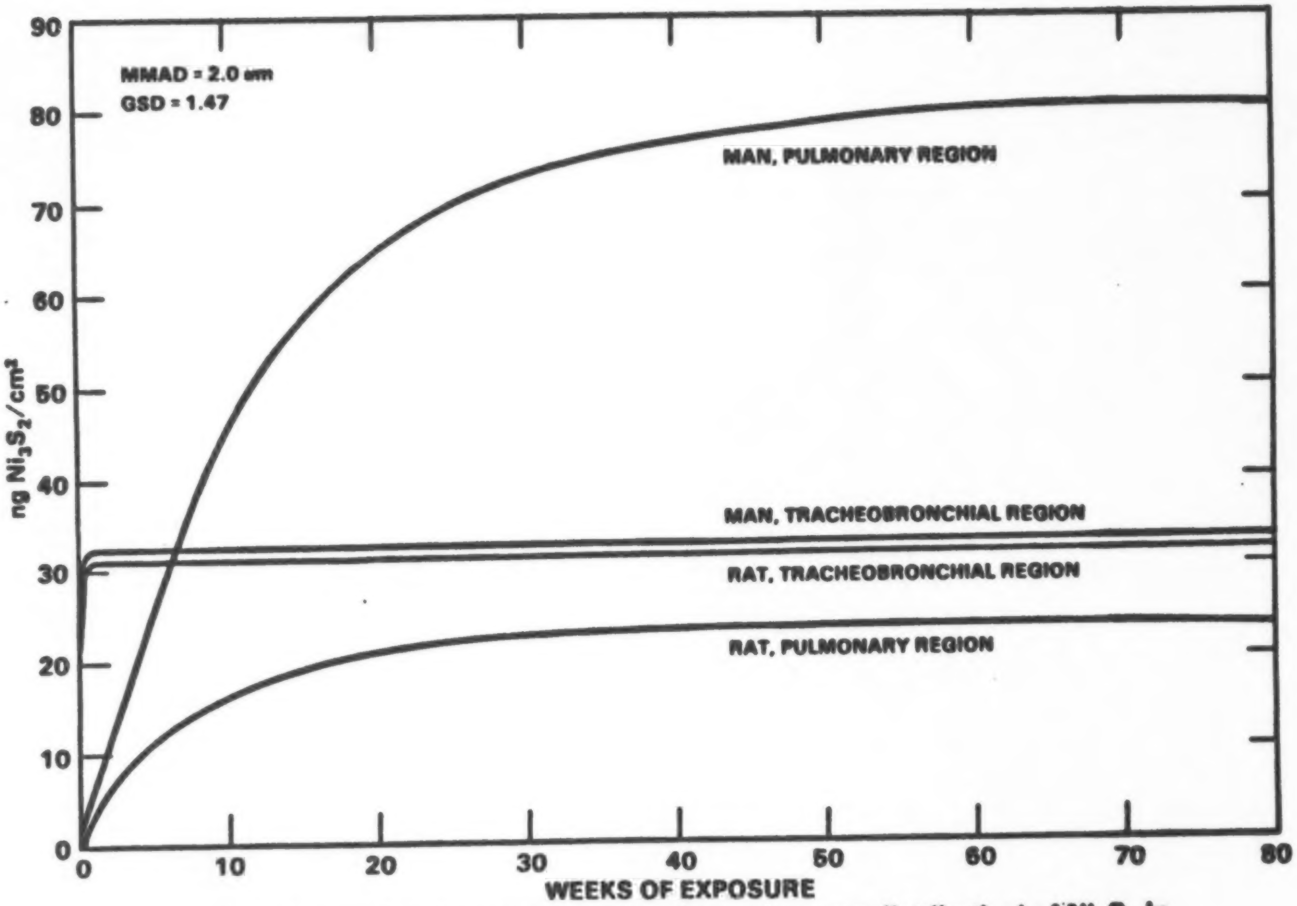

Figure 8-5. Accumulated surface area dose (assuming even distribution) of Ni_3S_2 in pulmonary and tracheobronchial regions of rat and man during continuous exposure for 78 weeks.

and 0.0116 ($T_{1/2}$ = 60 days) for man. Although there is evidence that inert particles are cleared in two phases from the pulmonary region (Bailey et al., 1985a,b; Philipson et al., 1985), this is not considered for nickel subsulfide in these calculations.

Figure 8-5 shows that under these assumptions and the exposure conditions of the study by Ottolenghi et al., steady state levels are reached for both the tracheobronchial and pulmonary regions within the 78-week period. Equilibrium levels for the tracheobronchial region are very similar for the rat (32.6 ng/cm^2) and for man (31.4 ng/cm^2). The main difference between the rat and man is in the accumulated surface area dose of the pulmonary region which is considerably higher in man (equilibrium value = 80.2 ng/cm^2) than in the rat (equilibrium value = 23.3 ng/cm^2).

Calculation of a nickel subsulfide exposure concentration for humans for 6 hours/day, 5 days/week that would accumulate to the same equilibrium as that for the rat (23.3 ng/cm^2) gives a value of 282 μg/m^3. This means, under the assumptions made for pulmonary retention of inhaled nickel subsulfide in rats and man, that humans will reach the same pulmonary surface concentration when exposed to a 3.5-fold lower concentration than rats (at a nickel subsulfide particle size of 2.0 μm). Even if it is assumed that rats and man have the same pulmonary retention half-time, the human exposure concentration necessary to reach the same equilibrium value would still be only half (470 μg/m^3) of the 970 μg/m^3 used in the rat study.

If the exposure of humans is continuous, i.e., 24 hours/day for a lifetime, then the exposure concentration decreases to 70.5 μg/m^3 in reaching a pulmonary equilibrium value of 23.3 ng/cm^2. This is about 1/14 of the concentration used in the study by Ottolenghi et al. (1974).

Figure 8-5 shows that tracheobronchial surface area accumulation is very similar in rat and man for this particle size and a GSD of 1.47, i.e., the exposure concentration to reach equilibrium (32 ng/cm^2) is about the same in both species (970 μg/m^3 for rat versus 1005 μg/m^3 for man). Under constant 24-hour exposure conditions, the equilibrium value for tracheobronchial surface area dose (32 ng/cm^2) would be reached at a fourfold lower exposure concentration of about 250 μg/m^3. This is about 3.5 times higher than the predicted inhaled concentration necessary to reach the equilibrium of the pulmonary surface area dose calculated in the preceding paragraph.

Table 8-36 summarizes the above results and presents the equivalent exposure values for humans to receive the same daily deposited dose per surface area and equilibrium values per surface area as the rat. As can be seen, the human and rat exposures are nearly equal for tracheobronchial dose, but humans require significantly less exposure for equal pulmonary dose. In order to combine the tracheobronchial and pulmonary regions (the Ottolenghi et al. study described tumors in both regions), the assumption was made of dose/surface area equivalence between the two regions. Regions were then combined on the basis of combined dose/combined surface area. The results show 636 $\mu g/m^3$ and 284 $\mu g/m^3$ as human equivalent exposures for daily deposited dose/surface area and equilibrium dose/surface area, respectively.

8.3.2.4 Calculation of the Incremental Unit Risk Estimates. The incremental unit risk extrapolations from rat to man using the human equivalent exposures calculated in the two previous sections are presented in Table 8-37. The unit risks are calculated using GLOBAL83. The human equivalent continuous exposure for the deposited daily dose/surface area and the equilibrium dose/surface area are calculated from data provided in Section 8.3.2.3.2 as follows:

$$636\ \mu g/m^3 \times \frac{6}{24} \times \frac{5}{7} \times \frac{78}{110} = 80.5$$

The results are close for all three methods, with the general method of dose equivalence on a mg/bw$^{2/3}$ basis providing an estimate between the other two. The maximum likelihood estimates range from 1.8×10^{-3} to 4.1×10^{-3} $(\mu g/m^3)^{-1}$, with the upper limits ranging from 2.7×10^{-3} to 6.1×10^{-3} $(\mu g/m^3)^{-1}$. As will be shown next, these estimates are approximately one order of magnitude greater than those obtained based on human studies.

8.3.2.5 Interpretation of Quantitative Risk Estimates. For several reasons, the unit risk estimate is only an approximate indication of the absolute risk in populations exposed to known concentrations of a carcinogen. First, there are important host factors, such as species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, and disease states. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to

TABLE 8-36. DAILY DEPOSITED SURFACE AREA (SA) DOSE, CLEARANCE HALF-TIME (T 1/2), EQUILIBRIUM VALUES AT 78 WEEKS, AND TOTAL ACCUMULATED DOSE MODELED IN RAT AND IN MAN UNDER EXPOSURE CONDITIONS OF THE OTTOLENGHI et al. (1974) STUDY: FOR TRACHEOBRONCHIAL (TB), PULMONARY (P), AND COMBINED REGIONS

	Rat			Human				
							Equivalent exposure by[c]	
Region	Daily deposited dose/SA[a] (ng/cm^2)	$T_{1/2}$ (days)	Equilibrium values[b] (ng/cm^2)	Daily deposited dose/SA[a] (ng/cm^2)	$T_{1/2}$ (days)	Equilibrium values (ng/cm^2)	Daily deposited dose/SA (μg/m^3)	Equilibrium dose/SA (μg/m^3)
TB	39.52	0.8	32.6	38.12	0.8	31.4	1005	1007
P	0.63	36	23.3	1.30	60	80.2	470	282
Combined[d]	1.03	--	23.4	1.57	--	79.8	636	284

[a] Dose deposited for 970 μg/m^3 exposure of 6 hours/day.

[b] A_t = (daily deposited dose) x (5/7)/b, where b = ln 2/$T_{1/2}$ for TB and P.

[c] Assuming exposure of 6 hours/day and 5 days/week.

[d] Combined on the basis of combined (TB + P) dose/combined (TB + P)SA.

TABLE 8-37. INCREMENTAL MAXIMUM LIKELIHOOD AND UPPER-LIMIT UNIT RISK ESTIMATES FOR RAT-TO-HUMAN EXTRAPOLATION USING THE OTTOLENGHI et. al. (1974) RAT INHALATION STUDY OF NICKEL SUBSULFIDE AND THE ONE-HIT MODEL

Equivalence method	Human equivalent continuous exposure ($\mu g/m^3$)	Incremental unit risk estimates: Maximum likelihood $(\mu g/m^3)^{-1}$	Upper-limit $(\mu g/m^3)^{-1}$
$mg/bw^{2/3}$	46.1	3.2×10^{-3}	4.8×10^{-3}
Deposited daily dose/SA[a]	80.5	1.8×10^{-3}	2.7×10^{-3}
Equilibrium dose/SA[a]	36.0	4.1×10^{-3}	6.1×10^{-3}

[a] Surface area of the lung.

genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent compared with other carcinogens. The comparative potency of different agents is more reliable when the comparison is based on studies in the same test species, strain, and sex, and by the same route of exposure.

The quantitative aspect of the carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., setting regulatory priorities, or evaluating the adequacy of technology-based controls. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk; i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower. The risk estimates presented in subsequent sections should not be regarded as accurate representations of the true cancer risks even when the exposures are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper limits of risk is found to be useful.

8.3.2.6 Alternative Methodological Approaches. The methods presented in the Proposed Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 1984) and followed by the CAG for quantitative assessment are consistently conservative, i.e., avoid underestimating risks. The most important part of the methodology contributing to this conservatism is the linear nonthreshold extrapolation model. There are a variety of other extrapolation models which could be used, most of which would give lower risk estimates. In other documents, other models have been used for comparative purposes only. However, the animal inhalation data for nickel have only one dose group plus a control; these limited data do not allow estimation of the parameters necessary for fitting these other models.

The position taken by the CAG is that the risk estimates obtained by use of the linear nonthreshold model are upper limits and the true risk could be lower.

With respect to the choice of animal bioassay data as the basis for extrapolation, the present approach is to use the most sensitive responder. Alternatively, the average responses of all the adequately tested bioassays could be used. Again, with only the one positive nickel subsulfide study, the data are too limited for alternative approaches.

8.3.3 Quantitative Risk Estimates Based on Epidemiologic Data

Epidemiologic studies have shown strong evidence that secondary smelting and refining of nickel sulfide ores by pyrometallurgical refining processes cause nasal and respiratory tract cancers in exposed workers. However, the extensive review in this document of epidemiologic data on nickel has not produced sufficient evidence for the estimation of incremental unit risk values for any nickel compounds except nickel subsulfide and nickel refinery dust. This lung and nasal cancer effect seen only for these latter nickel compounds might be partially or mostly explained by the formerly high dust and nickel subsulfide levels at refineries (up to 40 million times ambient levels of total nickel and approximately 1,000 times the nickel levels recorded in some occupational studies of workers not exposed to nickel subsulfide). However, some of these non-nickel subsulfide nickel exposures were 10,000 to 1,000,000 times those of ambient nickel levels but still showed no significant cancers (Egedahl and Rice, 1984; Cox et al., 1981; Cragle et al., 1984; Redmond et al., 1983, 1984). Conclusions from these studies, however, were limited by other considerations detailed in Section 8.1. Furthermore, the Roberts et al. (1982, 1984) studies comparing the sintering (including calcining and leaching) and non-sintering workers at Port Colborne and Sudbury, Ontario, isolated all the increased lung cancer among the sinter workers.

The one apparent contradiction to the hypothesis that the pyrometallurgical process and nickel subsulfide exposures are responsible for the observed cancer increase is the high cancer response in the electrolytic tankhouse workers observed in Kristiansand, Norway (Pedersen et al., 1973, 1979; Magnus, 1982). Here, workers exposed to nickel sulfate, nickel metal, copper-nickel oxides, and nickel chloride showed large increases in both lung and nasal cancer. These increases were not observed, however, in the electrolysis operations at Port Colborne, Ontario (Roberts et al., 1984; International Nickel Company, Inc., 1976). Sutherland (1959) reported an increase in lung cancer among electrolytic workers at Port Colborne, but the subsequent analyses of updated results confirmed that the increase was limited to the sintering, leaching, and calcining areas of the refinery.

Public comments to a draft of this document suggested that the electrolysis operation at Kristiansand "probably created a much higher concentration of nickel sulfate aerosols than would have existed in the Port Colborne tankhouse" (International Nickel Company, Inc., 1986). In additional comments submitted by Falconbridge Ltd., a table (Falconbridge, 1986) showed that the concentrations of fine solids per unit volume of nickel-bearing electrolytes in Kristiansand was about eight times that in the electrolysis department at Port Colborne in 1954. Factoring in the information that the total tonnage of electrolytes at Kristiansand was nearly three times that of Port Colborne, the commentators suggest that this increased concentration may provide "a possible explanation for the apparent divergence in frequency of respiratory cancer in the two plants." Furthermore, the comments of Falconbridge presented a reading of 40 mg Ni/m^3 in one area of the Kristiansand electrolysis department which the commentators attributed to a 50 percent insoluble and 50 percent soluble form. The Environmental Protection Agency is presently further analyzing these tankhouse data, but the results are not yet available.

The following is an analysis of the epidemiologic data available for a quantitative assessment of risk from exposures to nickel refinery dusts. In Section 8.3.3.1.2, the dose-response data available for a choice of model are evaluated. In Section 8.3.3.2, the models are used to estimate the quantitative risk for several available data sets. Data sets from nickel refineries in Huntington, West Virginia; Copper Cliff, Ontario; Clydach, Wales; and Kristiansand, Norway are examined because they possess information available either for choice of model or for separation of risk by the type of nickel exposure. The dose-response information from Port Colborne (Roberts et al., (1984) is not presented here because its analysis produces results very similar to that of Copper Cliff.

8.3.3.1 Choice of Epidemiologic Models: Investigation of Dose-Response and Time-Response Relationships for Lung Cancer

8.3.3.1.1 Description of basic models. The choice of a model for risk extrapolation from human studies always involves many assumptions, primarily because the data are very limited for quantitative analysis. Two assumptions are nearly always necessary:

(1) Response is some function of some cumulative dose or exposure.

(2) The measure of response, either the excess risk or the relative risk, is a linear function of that cumulative exposure.

For particulates such as nickel subsulfide and nickel refinery dust with relatively long lung clearance times, the assumption of a cumulative exposure-response is probably a close approximation to actual lung burden. Furthermore, cumulative exposures are generally the only data available. With respect to model, assumption (2) leads to a choice of two models:

(A) The excess additive risk model. This model follows the assumption that the excess cause-age-specific rate due to nickel exposure, $h_1(t)$, is increased by an amount proportional to the cumulative exposure up to that time. In mathematical terms this is $h_1(t) = \Delta X_t$, where X_t is the cumulative exposure up to time t, and Δ is the proportional increase. The total cause-age-specific rate h(t) is then additive to the background cause-specific rate $h_0(t)$ as follows:

$$h(t) = h_0(t) + h_1(t)$$

Under the assumptions of this model, we can estimate the parameter Δ by summing the expected rates to yield:

$$E_j = E_{0j} + \Delta X_j W_j$$

where E_j is the total number of expected cases in the observation period for the group exposed to cumulative exposure X_j. E_{0j} is the expected number of cases due to background causes; it is usually derived from either county, state, or national death rates, corresponding to the same age distribution as the cohort at risk. W_j is the number of person-years of observation for the j^{th} exposure group, and the parameter Δ represents the slope of the dose-response model. To estimate Δ, the observed number of cause-specific deaths, O_j, is substituted for E_j.

(B) The multiplicative or relative risk model. This model follows the assumption that the background cause-age-specific rate at any time is increased by an amount proportional to the cumulative dose up to that time. In mathematical terms this is $h(t) = h_0(t) \times (1 + \Delta X_t)$. As above, we can estimate the parameter Δ by summing over the observed and expected experience to yield:

$$\frac{E_j}{E_{0j}} = 1 + \Delta Xj$$

E_j is estimated by the observed deaths, O_j, and the equation is solved for Δ. O_j/E_{0j} is the standardized mortality ratio (SMR).

In many previous quantitative risk assessments, the Environmental Protection Agency has used the relative risk model in the form

$$B_H X = P_0(\text{SMR} - 1)$$

where X is the average dose to which an individual is exposed from birth throughout life, and P_0 represents the lifetime background cause-specific risk. The two formulations are approximately equal if one sets

$$\Delta = B_H/P_0 \text{ and } X = \Sigma X_j \cdot N_j/(70 \cdot \Sigma N_j)$$

where N_j is the number of men exposed at level X_j. The multiplicative model is one in which the SMR is linearly related to dose. It assumes that the time-response relationship is constant; that is, at any time since the start of exposure (after a latent period), the SMR for a set cumulative exposure is constant. Likewise, in the additive model, the excess mortality rate for a set cumulative exposure is constant over time. Under either the multiplicative or additive model, excess risk (SMR or mortality rates, respectively) remains constant once exposure ceases. As indicated below, this result is important in determining which of these models holds for respective nickel data sets.

8.3.3.1.2 Investigation of data sets. Investigated in the following sections are four data sets for nickel refinery workers in which there is some evidence for the use of a dose-response model for risk assessment. In addition to dose-response, differences due to exposures to different nickel compounds are compared. The workers at the Huntington, West Virginia refinery are subdivided into those with nickel subsulfide exposure versus those whose job exposures should not have included the subsulfide form. This separation with dose-response data does not exist in the other refineries. Although the Roberts et al. (1984) study clearly shows refinery dust with nickel subsulfide as being carcinogenic, the analysis is confounded by the fact that refinery dust and nickel subsulfide exposures were at such high levels compared to the rest of the plant. Only the Enterline and Marsh (1982) data appear to have lower subsulfide levels, by which dose-response can be compared with the non-subsulfide-exposed workers. The dose-response curves for nasal sinus cancer will not be investigated, since nasal sinus cancer risk from nickel is thought to be only an occupational hazard associated with the pyrometallurgical process.

8.3.3.1.2.1 Huntington, West Virginia. The study of mortality in West Virginia nickel (pyrometallurgical) refinery workers by Enterline and Marsh (1982) showed a dose-response with cumulative nickel exposure versus lung cancer. These results are reproduced (eliminating the nasal sinus cancers) in Table 8-38. Although there are only eight respiratory cancer deaths (ICD 161-163; there were also two nasal cancer deaths, not included) in the refinery workers (as defined by employment of 1+ years in the calcining or casting and melting department) versus 7.55 expected, the data represent an important attempt at finding a dose-response relationship in one of the less dusty of the nickel refineries. One significant feature of the data in Table 8-38 is that the dose is based on a cumulative exposure of up to 20 years, while response allows a 20-year latent period from first exposure.

Verification of the above dose-response models can be done in several ways. As a first approach, weighted regression fits (for the refinery data only) were attempted on the observed SMRs using the expected deaths as weights. The weighted regression technique merely allows more weight where there are more expected deaths. Statistically, it stabilizes the variances of the SMRs, which allows the standard regression estimation techniques to be used.

TABLE 8-38. WEST VIRGINIA NICKEL REFINERY AND ALLOY WORKERS (NON-REFINERY)[a]: OBSERVED AND EXPECTED DEATHS FROM LARYNX AND LUNG CANCER (ICD 161-163) AND SMR FOR MALE NICKEL WORKERS 20 YEARS AFTER FIRST EXPOSURE BY CUMULATIVE NICKEL EXPOSURE UP TO 20 YEARS FROM ONSET OF EXPOSURE (ALSO INCLUDES REGRESSION FITS FOR TWO MODELS)

Cumulative nickel exposure mg Ni/m³ mo. (mean X)	Refinery[a] (all hired before 1947)				Non-refinery									
					(hired before 1947[b])				(hired after 1946[c])			All non-refinery workers		
	Observed	Expected	O/E	$\frac{O-E}{PY}$[d]	Observed	Expected	O/E	$\frac{O-E}{PY}$	Observed	Expected	O/E	Observed	Expected	O/E
<10 (4.20)	0	0.04	0	-0.00136	9	13.22	0.681	-0.0005279	1	2.70	0.37	10	15.92	0.628
10-24 (18.89)	0	0.34	0	-0.00152	15	13.26	1.13	0.0002194	3	1.66	1.81	18	14.92	1.206
25-49 (39.03)	0	1.00	0	-0.001742	9	10.35	0.87	-0.0002281	0	1.24	0	9	11.59	0.777
50-99 (64.37)	3	3.08	0.974	-0.0000431	10	4.43	2.26	+0.0023166	0	0.53	0	13	4.96	2.621
100-199 (160.91)	1	0.61	1.64	0.0011611	4	5.35	0.748	-0.0004528	0	0.14	0	5	5.49	0.911
≥200 (563.80)	4	2.48	1.61	0.001041	None at risk				None at risk			None at risk		
Linear regressions	(weighted)				(unweighted)				--			(unweighted)		
Multiplicative model:	SMR = 0.413 + 0.00259X				SMR = 1.15 - 0.0002X							SMR = 1.16 + 0.0012X		
	$r = 0.82$ ($p < 0.05$)				$r = -0.019$ N.S.							$r = 0.090$ N.S.		
Additive model:	$\frac{O-E}{PY} = 0.00017+1.74x10^{6}X$				$\frac{O-E}{PY} = 0.000712+4.1x10^{6}X$							$\frac{O-E}{PY} = 0.000301+1.7x10^{6}X$		
	$r = 0.55$ N.S.				$r = -0.232$ N.S.							$r = 0.079$ N.S.		

[a] Number at risk = 259; person-years at risk = 4,501.4.

[b] Number at risk = 1,533; person-years at risk = 27,227.8.

[c] Number at risk = 1,287; person-years at risk = 6,359.7.

[d] See Tables 8-47 and 8-48 for the person-years (PY).

Source: Enterline and Marsh (1982).

The results of the regressions are presented in Table 8-38. For the refinery data, the regression of SMR versus dose results in a statistically significant ($p < 0.05$) dose-response, while there was no dose-response relationship for the non-refinery workers, whether hired before 1947 (a subcohort comparable in years of follow-up and expected background rates to the refinery workers), after 1946 (when the refinery was torn down), or combined. These results are suggestive of a linear relationship with the SMR for the refinery workers versus the non-refinery workers. For the additive risk model, neither data set showed a statistically significant dose-response trend.

8.3.3.1.2.2 Copper Cliff, Ontario. Another data set that suggests a linear relationship between SMR and cumulative dose for nickel pyrometallurgical refinery workers is that of 495 workers at the Copper Cliff, Ontario plant (Chovil et al., 1981). The Copper Cliff refinery, using the same pyrometallurgical process and nickel matte from the same region as that shipped to the West Virginia refinery, operated from 1948 to 1963. A total of 54 lung cancer cases and 37 deaths occurred, versus 6.38 expected cases and 4.25 expected deaths. The standardized incidence ratio (SIR) and SMR were 8.5 and 8.7, respectively.

The shortcomings of the Chovil et al. study, which provide potential biases, have been discussed in Section 8.1.2.1.4. The methods used for obtaining the observed and deriving the expected lung cancer cases make the incidence data less reliable than the mortality results. The poor follow-up of only 75 percent of the cohort biases the results toward underestimating the risk, since all those lost to follow-up were considered survivors for the mortality analysis and noncancer cases for the incidence analysis. The emphasis in the following analyses is on the mortality data, which are considered the more accurate because of reasons discussed above. The group most biased by the large percentage lost to follow-up is felt to be those exposed earliest and to the dustiest conditions. Counting these as survivors would tend to bias the slope estimate downwards. Thus, the risk estimates derived from the Chovil et al. data would have to be considered a lower limit of the risks that did occur.

In analyzing these data for dose-response relationships, the Chovil et al. (1981) study provided no measure of exposure levels, but described conditions as being "extremely dusty." The authors also provided a reference suggesting that "actual dust levels might have dropped by half" after 1951 and "thus it was thought that it would be appropriate to weight exposure for men employed during the period 1948 to 1951 by multiplying these exposures by a factor of two for purposes of dose-response analysis." [Roberts et al. (1984) analyzed the 37 lung cancer deaths also and found a highly significant linear trend with unweighted duration of exposure. The authors' numbers, however, are somewhat different than those of the Chovil et al. study presented here.]

Table 8-39 presents the lung cancer incidence and deaths during the study follow-up period from January 1963 through December 1978. Since exposure ceased in 1963, both models assume that excess risk remains constant during the follow-up period. Weighted exposure is presented as cumulative years of exposure where exposure during any of the first four years was weighted double (see below). The authors grouped the exposure years so that there were roughly equal numbers of men (and hence approximately equal expected incidences and deaths) in each of the seven groupings. This eliminated the need to use a weighted analysis.

The results of the analysis show a highly statistically significant ($p < 0.005$) linear regression between both the SMR and SIR and cumulative exposure (since person-years of observation are not given in the paper, only the multiplicative risk model can be investigated). The results are basically identical; either one provides strong evidence for the linear dose-response relationship, with the deviations from linearity not statistically significant. Other factors must be considered in the above analysis. In addition to the dose-response analysis, Chovil and co-workers (1981) discussed the distribution of cases by year of first employment. They noted that all but one of the 37 lung cancer deaths and all of the nasal cancer cases occurred in the subgroup first employed from 1948 through 1951. This part of the analysis has been extended in a recent paper by Muir et al. (1985), who presented results on a larger Copper Cliff cohort (all workers with any exposure versus a stratified random sample of workers with at least five years total service with the company in the Chovil et al. study). The results of the Muir et al. (1985) analysis, presented in Table 8-40, show increased lung cancer mortality not only by duration of exposure, but also for the early exposure cohort versus the late exposure cohort. For the cohort exposed before 1952, the SMRs by duration of exposure are from 2.1 to 5.1 times those of the later cohort.

A partial explanation for these differences lies in the fact that the earlier cohort was followed longer (28 versus 25 years mean follow-up since first

TABLE 8-39. COPPER CLIFF REFINERY WORKERS: LUNG CANCER INCIDENCE AND DEATHS (ICD 162) BY SEVEN WEIGHTED DURATION OF EXPOSURE SUBGROUPS, FOLLOW-UP FROM JANUARY 1963 TO DECEMBER 1978

	Weighted exposure (years)							
	<1 (0.5)[a]	1-(2)	3-(4)	5-(6.5)	8-(9.5)	11-(12.5)	≥14(16)	Total
Number of men in subgroups (N_j)	67	78	82	77	70	66	65	495
Cases of lung cancer								
Observed	0	2	3	7	10	16	16	54
Expected	0.71	0.54	0.81	0.90	1.02	1.14	1.26	6.38
O/E	0	3.70	3.70	7.78	9.80	14.0	12.70	8.46
Linear regression								
(O/E) = a+b·(years)			a = 1.07	b = 0.87[c]		linear correlation coefficient r = 0.953[c]		
(O/E 1) = b·(years)			--	b = 0.87[c]		linear correlation coefficient r = 0.983[c]		
Lung cancer deaths								
Observed	0	0	3	4	6	13	11	37
Expected	0.47	0.36	0.54	0.60	0.68	0.76	0.84	4.25
O/E	0	0	5.56	6.67	8.82	17.11	13.10	8.70
Linear regression								
(O/E) = a+b·(years)			a = -0.18	b = 1.03[b]		linear correlation coefficient r = 0.921[b]		
(O/E - 1) = b·(years)			--	b = 0.92[c]		linear correlation coefficient r = 0.96[c]		

[a] Numbers in parentheses are estimated midpoints used in regression calculations.

[b] $p < 0.005$.

[c] $p < 0.001$.

Source: Chovil et al. (1981).

TABLE 8-40. COPPER CLIFF SINTER PLANT: LUNG CANCER MORTALITY 15 TO 29 YEARS SINCE FIRST EXPOSURE BY WORKERS FIRST EXPOSED BEFORE AND SINCE 1952, BY DURATION OF EXPOSURE

Years of sinter exposure	First sinter plant exposure						SMR ratio
	Before 1952			After 1952			$\left[\frac{\text{before 1952}}{\text{1952 or later}}\right]$
	Obs.	Exp.	SMR	Obs.	Exp.	SMR	
<5	23	7.76	296	3	2.15	139	2.1
5-9	11	0.64	1730	1	0.30	339	5.1
10+	18	1.51	1197	1	0.23	431	2.8
All	52	9.91	525	5	2.68	187	2.8

Mean	Before 1952	After 1952
Age at entry	27	24
Years of exposure	2.4	1.8
Years of follow-up	28	25

Source: Muir et al. (1985).

exposure), and that the average length of exposure was 33 percent higher (2.4 years versus 1.8 years). Even more significant is the average amount of nickel exposure before and after 1952. Chovil et al. (1981) hypothesized that the exposure of the early subcohort on a mg/m^3 basis was twice as high as that of the later cohort, but examination of a chart in a paper by Warner (1984) appears to put that ratio closer to three and possibly as high as five or six. Calculating a weighted linear regression (with the square root of expected as weights) of SMR versus years of exposure (with years of exposure before 1952 counted as double), the slope is significant at the $p = 0.05$ level, while deviations from linearity were not statistically significant. Factoring in all these data in a qualitative way further supports the dose-response relationship of SMR as being linear with cumulative dose.

The Copper Cliff results can be compared with those of the West Virginia refinery subcohort, since both subcohorts comprised workers exposed mostly in the higher risk nickel subsulfide areas. While the dust levels and lung cancer relative risks were much higher in the Copper Cliff plant, both dose-response relationships appear linear, indicating that the functional relationship spans a broad range of nickel (subsulfide) exposure.

8.3.3.1.2.3 Clydach, Wales. The Copper Cliff results must also be compared with results for the refinery workers in Clydach, Wales. The similarity between Copper Cliff and Wales in very high lung cancer relative risks (about 10 for workers starting before 1915, and about 6 for workers starting between 1915 and 1924), and in the apparent termination of exposure to the carcinogens in both plants, allows for comparisons of the effect of decreased exposure and for investigation of the effect of stopping exposure on the relative risk. In Copper Cliff, exposure ceased by 1963, whereas in Clydach, the relative risks decreased significantly for cohorts entering after 1925 and were not statistically elevated for those entering after 1930, indicating that exposure to the carcinogen was, at least, drastically reduced. These reductions seem to be concurrent with better industrial hygiene conditions.

Dose-response data from Clydach are presented several ways, and inferences can be made from these. Data by Doll et al. (1977), Table 8-41, present lung cancer mortality by year of first employment. As can be seen, the relative risk steadily declines from 10.0 for the subcohort first exposed before 1910 to 2.5 for the subcohort first exposed between 1925 and 1929. This is consistent with

TABLE 8-41. CLYDACH, WALES NICKEL REFINERY WORKERS: TOTAL MORTALITY AND CANCER MORTALITY BY YEAR OF FIRST EMPLOYMENT

Year of first employment	Number of men	Person-years at risk	Average years at risk[a]	Number of deaths		Lung cancer deaths		
				Observed (%)	Expected	Observed (%)	Expected	Ratio
Before 1910	119	1980.0	16.6	117(98)	102.01	24(20)	2.389	10.0
1910 - 1914	150	2666.5	17.7	137(91)	92.84	34(23)	3.267	10.4
1915 - 1919	105	2204.0	21.0	89(85)	55.44	20(19)	3.070	6.5
1920 - 1924	285	7126.5	25.0	209(73)	146.25	50(18)	9.642	5.2
1925 - 1929	103	2678.0	26.0	60(58)	51.91	9(9)	3.615	2.5
All periods before 1930	762	16,655	21.9	612(80)	448.45	137	21.983	6.2
1930 - 1944	205	4,538.0	22.1	77(38)	60.42	8	5.463	1.5
All periods	967	21,193.5	22.0	689(71)	508.87	145	27.446	5.3

[a] Between the years 1934 and 1971. For the two early subcohorts, the person-years at risk start after the 20-year latent period.

Source: Doll et al. (1977).

the relative risk functionally related to cumulative dose, since each subcohort is probably exposed for five years longer than the one succeeding it. It is also consistent with the Copper Cliff results (Table 8-40), where the early subcohort exhibited higher lung cancer mortality than the later one.

The other Clydach data suitable for analysis of dose-response relationships come from Peto et al. (1984). These data, taken from a slightly different cohort than those of earlier studies on Clydach refinery workers, categorize men by duration of exposure in the calcining furnaces. The results, presented in Table 8-42, show that lung cancer deaths rise significantly ($p < 0.05$) in a linear way with increasing years in the calcining furnaces.

Peto et al. (1984) present dose-response relationships for lung cancer mortality in terms of low versus high exposure, with breakdowns of each. The results, shown in Table 8-43, clearly show increased relative risk with increased duration of exposure.

Peto et al. (1984) also attempt to combine data so that many factors are introduced simultaneously into a dose-response model. In order to do this, they had to review individual records, not only for vital status but also for four other factors: age first exposed, year first exposed, time-since-first-exposure, and exposure in high-risk jobs. The factors were put into a Poisson model in which the expected values, the expected cause-specific death rates, were defined as a multiplicative function of the four factors (see Table 8-3). Based on this additive form of the risk model, Peto and co-workers found both time-since-first-exposure and the high exposure categories to be highly significant ($p < 0.001$) after adjusting for the other factors. The analysis also found age at, and period of, first exposure not significant. The nonsignificance of period of first exposure is a curious and probably misleading result, considering the lung cancer relative risk ratios in Table 8-41. It is quite probable that period of first exposure is just too highly correlated with exposure level as defined by duration in high-risk categories, and that if one factor is dropped from the model, the other shows high statistical significance. Since this is a survivor cohort starting in 1934, those first employed earlier should be the same people, with longer and probably higher cumulative exposure.

One factor that is consistent for the Clydach lung cancer data is that relative risk decreased with time since entry. While the possible confounding of these time factors has been discussed above and in Section 8.1.1.7, we discuss it at this point vis-a-vis the dose-response model. The significance of

TABLE 8-42. CLYDACH, WALES NICKEL REFINERY WORKERS: LUNG CANCER MORTALITY BY DURATION OF YEARS IN CALCINING FURNACES BEFORE 1925 (CHI-SQUARE TESTS)

	Years in calcining furnaces			
Lung cancer deaths	0	1-2	3+	Total
Yes	116	13	8	137
No	489	39	14	542
Total (percent)	605 (19.2)	52 (25.0)	22 (36.4)	679 (20.2)
Total chi square	$\chi_2^2 = 4.71$ $0.05 < p < 0.10$			
Test for linear trend	$\chi_1^2 = 4.53$ $p < 0.05$			
Departure from linearity	$\chi_1^2 = 0.18$ N.S.			

Source: Adapted from Peto et al. (1984).

TABLE 8-43. CLYDACH, WALES NICKEL REFINERY WORKERS: LUNG CANCER MORTALITY BY TYPE AND DURATION OF EXPOSURE FOR MEN FIRST EMPLOYED BEFORE 1925

	Years in furnaces	Years in $CuSO_4$	Number of men	Lung cancer deaths		
				Observed	Expected	O/E
Low exposure	0	0	404	64	19.00	3.4
	0	<5	99	21	4.12	5.1
High exposure	0	5+	50	15	1.08	13.9
	<2	0	63	17	1.51	11.2
	2-5	0	45	14	0.80	17.5
	5+	0	18	6	0.32	18.8
Total			679	137	26.83	5.1

Source: Peto et al. (1984).

this time-since-entry factor is that the relative risk (or proportional hazards) model assumes that (and is only valid if) the risk ratio (SMR) is constant over time. The results, shown in Table 8-44 for the Peto and Kaldor data, are similar to results first shown by Doll et al. (1970), who discussed this decline. Doll's explanations were: (1) that the men most heavily exposed would die sooner, so that the survivors would actually be those who were less heavily exposed; and (2) that the effect of nickel is lessened over time. However, an additional explanation is related to the fact that (a) the nickel concentration was so high that 20 percent of the cohort died of lung cancer, and (b) the normal age-specific incidence of lung cancer (for cigarette smokers) rises to the fourth power of age, anyway (Doll and Peto, 1978). With such a high nickel exposure causing such a large rise in lung cancer mortality, maintaining such a high relative risk into old age would be close to impossible, especially if the competing risks of the older ages are considered. This decreasing relative risk over time-since-first-exposure might not be observed if the nickel concentration were not so high; also, the decrease was not statistically significant until 40 years after first exposure.

In contrast to the decreasing relative risk (Table 8-44), the excess risk increases with time, since exposure is statistically increased over the 0 to 19 years-since-entry group after adjusting for exposure. If the additive (excess risk) model were the proper model, then the excess risk should be constant over time, after adjusting for exposure. Again, however, an argument similar to the one above can explain the rise to a peak in the 30- to 39-year group followed by a decline. Neither model is completely supported or contradicted by the Clydach lung cancer data.

8.3.3.1.2.4 Kristiansand, Norway. The final data set for which inferences about a model can be made is from the nickel refinery at Kristiansand, Norway, the most recent update being that of Magnus et al. (1982). Although the data provide neither person-years nor dose-response relationships, there are three points worth discussing. The first is that, unlike the decrease seen in the Clydach data, the relative risk for lung cancer remained essentially constant (around 4) from 15 years through 35 years after first employment (Table 8-45). If conditions remained dusty through the early 1960s, then these figures do support a relative risk model despite the fact that they are unadjusted for nickel exposure. When these figures are adjusted for smoking, the relative

TABLE 8-44. CLYDACH, WALES NICKEL REFINERY WORKERS: LUNG CANCER MORTALITY BY TIME SINCE FIRST EXPOSURE FOR WORKERS EXPOSED BEFORE 1925[a]

Years since entry[a]	Person-years at risk	Lung cancer deaths		Relative risk O/E	Excess risk O - E
		Observed	Expected		Person-years
0 - 19	2,564.3	6	0.55	10.9	0.0021
20 -	4,757.1	35	3.14	11.1	0.0067[c]
30 -	4,326.2	55	7.59	7.2	0.0110[b]
40 -	2,461.4	31	9.20	3.4[b]	0.0089[b]
50+	1,076.4	10	6.37	1.6[b]	0.0034
Total	15,185.4	137	26.85	5.1	0.0073

[a] First year of observation was 1934, 10 years after the last person was first exposed. Thus, the 6 deaths in the 0-19 years-since-entry group all occurred before 1945, and the 0-19 years category cannot possibly include any of the subcohort whose first employment was before 1915.

[b] Significantly different ($p < 0.01$) vs. 0-19 years after adjusting for exposure, year, and age at first employment.

[c] Same as b, but with $p < 0.05$.

Source: Adapted from Kaldor et al. (1985, unpublished). According to one of the authors (Morgan), this paper is being revised, but the above information has been verified. Since other material was inaccurate pending this revision, Dr. Morgan requested that the review of this paper be removed from Section 8.1.

risk increases until 35+ years postexposure, after which it decreases but still remains significantly above the 3 to 14 year time-since-first-employment group.

The second point pertains to the authors' attempt to adjust for the effect of smoking and nickel exposure on lung cancer. The results shown in Table 8-46 indicate that the combined effect of nickel and smoking is greater than additive but less than multiplicative. Again, these analyses are not adjusted for nickel exposure within the refinery; it is assumed that smokers and nonsmokers

TABLE 8-45. KRISTIANSAND, NORWAY DATA: RATIO BETWEEN OBSERVED AND EXPECTED NUMBER OF CASES OF LUNG CANCER AMONG NORWEGIAN NICKEL WORKERS BEFORE AND AFTER ADJUSTMENT FOR SMOKING HABITS

	Number of years since first employment							
	3-14 years		15-24 years		25-34 years		35+ years	
Year of first employment	Unadj. ratio	Adj. ratio	Unadj. ratio	Adj. ratio	Unadj. ratio	Adj. ratio	Unadj. ratio	Adj. ratio
1916-1929	-	-	-	-	22.6	22.6	3.9	3.9
1930-1939	-	-	-	-	4.4	5.6	4.9	6.7
1940-1949	1.8	1.8	2.7	2.7	3.1	5.0	-	-
1950-1959	2.7	3.2	5.1	6.5	2.5	4.8	-	-
1960-1965	1.6	2.7	4.2	7.9	-	-	-	-
Total	2.3	2.7	4.0	6.7	4.1	8.0	4.3	5.6

Source: Magnus et al. (1982).

TABLE 8-46. KRISTIANSAND, NORWAY DATA: AGE-STANDARDIZED INCIDENCE OF CANCER OF THE LUNG AMONG NONSMOKERS AND SMOKERS IN A SAMPLE OF THE GENERAL POPULATION OF NORWAY AND AMONG EMPLOYEES AT THE NICKEL REFINERY

Group	Exposure to nickel	History of cigarette smoking	Number of lung cancer cases[a]	Age-adj. lung cancer rate	Difference vs. controls	Ratio vs. controls
Controls	No	No	9	0.19	0.0	1.0
Nickel workers	Yes	No	5	1.60	1.41	8.4
Controls	No	Yes	116	1.13	0.94	5.9
Nickel workers	Yes	Yes	39	3.27	3.08	16.2

[a] Sample covered cases from 1966-1977.

[b] Per 1,000 person-years.

Source: Adapted from Magnus et al. (1982).

within the refinery both experienced the same nickel exposure. Finally, the number of nonsmoking cases is small and no firmer conclusions can be drawn.

8.3.3.1.2.5 Conclusion--Choice of models. All analyses for which dose-response estimates for lung cancer can be calculated show a positive relationship, based on either an additive or multiplicative model, and can be considered to support either model. When time relationships are introduced, there is evidence both supporting and contradicting both models. The analyses by Peto et al. (1984) and by Kaldor et al. (1985, unpublished) supported a model less than multiplicative over background, in the sense that the relative risk decreases with time-since-first-exposure. On the other hand, both their analyses also showed that the (additive) excess risk increased with time-since-first-exposure. The Norwegian data reported by Magnus et al. (1982) also supported a model which was less than multiplicative but greater than additive when smoking was factored in as being the most important agent for non-nickel-induced lung cancer. However, in a separate analysis, Magnus et al. (1982) also reported a constant or increasing relative risk with time-since-first-exposure, which can be interpreted as supporting a relative risk model. In this part of the analysis, Magnus and co-workers did not report person-years exposed, so no estimates of excess risk can be derived. Therefore, for the four data sets analyzed below, both the additive and multiplicative excess risk models will be fit whenever possible.

8.3.3.2 Calculation of the Incremental Unit Risk from Human Data

8.3.3.2.1 Huntington, West Virginia.

8.3.3.2.1.1 Refinery workers. In extrapolating from occupational to low environmental risks due to nickel exposure, the search for the best data set focuses not on one that provides the greatest risk, but on one that might best approximate environmental conditions. This usually translates to choosing a data set (or sets) which shows dose-response at low exposures, and for which there is some reasonable measure of exposure. For the nickel refinery data, we have chosen the Huntington, West Virginia data set (Enterline and Marsh, 1982) as the primary data set for several reasons. First, International Nickel Company, Inc., (1976) reported that dust concentrations around the calciners were much lower than those at Clydach, Port Colborne, or Copper Cliff. Enterline and Marsh (1982) cited this and suggested that nickel exposures may have, thus, been considerably lower.

Second, the Huntington refinery was similar to the other refineries in operation and type of matte refined. Third, it was the only U.S. refinery, so that background rates were more relevant to an extrapolation to the U.S. environment. Fourth, nasal cancer rates were elevated, certainly indicating a significant exposure. Fifth, Enterline and Marsh's breakdown of the data and their analyses were more conducive to risk extrapolation than the other data sets. Enterline and Marsh broke their data set into three groups, with the refinery group being well-defined both by work location and time (the calciners were removed in 1947). Enterline and Marsh's refinery subcohort consisted of 266 men; 109 had worked in the calcining department for a year or more, and an additional 157 had worked in the physically adjacent melting and casting department, comprising 6,738.9 person-years at risk (average follow-up 25.3 years) after exposure had ceased. Enterline and Marsh also presented their data to adjust for a 20-year latent period from first exposure and to count exposure only up to 20 years from onset of exposure. These adjustments resulted in a subcohort comprised of 259 men and 4,501.4 person-years of risk after a 20-year latent period. Finally, the authors presented their exposure as mg Ni/m^3 months, units in which both amount and duration are incorporated.

The 259 refinery workers subcohort can be considered to have been exposed to nickel subsulfide. These can be compared directly with the 1,533 non-refinery workers who were assumed to have been exposed to nickel oxide but not nickel subsulfide.

Enterline and Marsh's data for lung cancer have already been presented in Table 8-38. The two basic models, the excess and the relative risk models, have also been presented above. The additive or excess risk model can be written as follows:

$$E_j = E_{0j} + \Delta X_j W_j \qquad (1)$$

where E_j is the number of expected lung cancer deaths in the observation period for the j^{th} group with cumulative exposure X_j, E_{0j} is the number of expected background lung cancer deaths, and W_j is the person-years exposed in the j^{th} group. The multiplicative model does not use person-years of observation directly in its formulation. It is

$$E_j = E_{0j}(1 + \Delta X_j) \qquad (2)$$

Under either assumed model, the observed number of deaths in the j^{th} exposure group is a Poisson random variable with mean E_j.

Solution for the estimate of Δ will be by the maximum likelihood method and will follow closely the development of the risk assessment model presented in the Updated Mutagenicity and Carcinogenicity Assessment of Cadmium (U.S. Environmental Protection Agency, 1985). For the additive risk model, the likelihood is

$$L = \prod_{j=1}^{6} e^{-[E_{0j} + \Delta X_j W_j]} [E_{0j} + \Delta X_j W_j]^{O_j} / O_j!$$

The maximum likelihood estimate (MLE) of the parameter Δ is obtained by solving the equation

$$\frac{d \ln L}{d\Delta} = \sum_{j=1}^{6} [- X_j W_j + \frac{O_j X_j W_j}{E_{0j} + \Delta X_j W_j}] = 0 \qquad (3)$$

for Δ.

The asymptotic variance for the parameter Δ is

$$-E\,[\frac{d^2 \ln L}{d^2\Delta}]^{-1} = [\sum_{j=1}^{6} \frac{X_j^2 W_j^2}{E_{0j} + \Delta X_j W_j}]^{-1} \qquad (4)$$

This variance can then be used to obtain approximate 95 percent upper and lower bounds for Δ. The refinery worker data used to obtain the estimate of Δ and its variance are presented in Table 8-47. The cumulative exposure is changed to a 24-hour equivalent times years exposure by the following factor:

$1\ (mg/m^3) \cdot$ months $= 1\ (mg/m^3) \cdot$ months x 1 year/12 months x $10^3 \mu g/1$ mg x 8/24 x 240/365

= 18.26 mg/m^3 continuous equivalent exposure

TABLE 8-47. DATA USED TO ESTIMATE Δ AND ITS VARIANCE: ENTERLINE AND MARSH "REFINERY WORKERS" SUBGROUP

Group cumulative exposure (mg Ni/m^3)·mo. (mean worker exposure)	Continuous µg/m^3 equivalent x years[a] X_j	Number at risk N_j	Person-years observation W_j	Background expected[b] E_{0j}	Observed lung cancer deaths O_j	X_jW_j	$X_jW_jO_j$
4.20	76.69	2	29.4	0.04	0	2,254.68	0
18.89	344.93	14	223.4	0.34	0	77,057.68	0
39.03	712.69	36	574.2	1.00	0	4.09×10^5	0
64.37	1,175.40	106	1,858.1	3.08	3	2.184×10^6	6.552×10^6
160.91	2,938.22	21	355.9	0.61	1	1.046×10^6	1.046×10^6
563.80	10,294.99	80	1,460.5	2.48	4	1.5036×10^7	6.0143×10^7
	15,542.92	259	4,501.4	7.55	8	1.8759×10^7	6.774×10^7

[a] Factor: 1 (mg/m^3) · months = 1 (mg/m^3) · months x 1 year/12 months x 10^3µg/1 mg x 8/24 x 240/365 = 18.26 (µg/m^3) x years continuous exposure.

[b] $\Sigma E_{0j} \cdot X_j = 31{,}777.16$.

Source: Enterline and Marsh (1982).

An estimate of $\hat{\Delta} = 9.66 \times 10^{-8}$ is obtained by rewriting equation (3) filling in the numbers from Table 8-47:

$$1.8759 \times 10^{7} = \frac{6.552 \times 10^{6}}{3.08 + \Delta(2.184 \times 10^{6})} + \frac{1.046 \times 10^{6}}{0.61 + \Delta(1.046 \times 10^{6})} + \frac{6.0143 \times 10^{7}}{2.48 + \Delta(1.5036 \times 10^{7})}$$

The Var $(\hat{\Delta})$ is estimated from equation (4) as 1.6×10^{-14} so that the S.E. $(\hat{\Delta}) = 1.28 \times 10^{-7}$ and the 95 percent upper and lower confidence limits (UCL and LCL, respectively) are approximately $\Delta_{UCL} = 3.07 \times 10^{-7}$ and $\Delta_{LCL} = 0$, respectively.

Alternatively, the estimate of Δ derived from the multiplicative model is obtained by solving the equation

$$\frac{d \ln L}{d\Delta} = \sum_{j=1}^{6} -E_{0j}X_j + \frac{O_jX_j}{1 + \hat{\Delta}X_j} = 0 \qquad (5)$$

for $(\hat{\Delta})$, which reduces to

$$31{,}777.16 = \frac{3{,}526.2}{1 + \hat{\Delta}(1{,}175.40)} + \frac{2{,}938.22}{1 + \hat{\Delta}(2{,}938.22)} + \frac{41{,}179.96}{1 + \hat{\Delta}(10{,}294.99)}$$

The solution to the above equation is $\hat{\Delta} = 5.70 \times 10^{-5}$.

The asymptotic variance for the estimate Δ of the multiplicative model is

$$- E \left[\frac{d^2 \ln L}{d^2\Delta}\right]^{-1} = \left[\sum_{j=1}^{6} \frac{E_{0j}X^2_j}{1 + \hat{\Delta}X_j}\right]^{-1} = 5.725 \times 10^{-9}$$

and the standard error is 7.57×10^{-5}, so that the 95 percent lower and upper bounds are 0 and 1.81×10^{-4}.

It becomes obvious from both of the above analyses that the asymptotic variances of the estimates are quite large for both models, leading to upper and lower bounds which encompass a broad range of values, including zero excess risk. This is due not only to the choice of models but also to the choice of the data set. Even though we expect it to provide the best low-exposure estimates of the various data sets because its exposures are closest to environmental exposures, the small sample size and relatively few person-years lead to large variances.

The fit of each model is shown in Table 8-48, and the likelihood ratio of the estimates, Δ, are evaluated for each model. Neither estimate is significantly different from zero.

8.3.3.2.1.2 Non-refinery workers. The Enterline and Marsh "non-refinery" subcohort excludes the refinery workers from the calcining, melting, and casting departments. As such, we can compare the results of the pre-1947 non-refinery subcohort with those of the refinery subcohort under the assumption that the actual nickel species differences by department are responsible for the differences in cancer responses. The "refinery" cohort is presumed to be exposed to a much higher proportion of the nickel subsulfide species. The pre-1947 non-refinery subcohort is used instead of the total non-refinery cohort, because the pre-1947 subcohort's background expected lung cancer death rates and years of follow-up (indicative of a similar age distribution) are nearly identical to those of the pre-1947 refinery cohort, while the background rates of the post-1946 cohort are considerably lower. Furthermore, the earlier group has 27,228 person-years of follow-up after a 20-year latent period, while the later group has only 6,360.

Table 8-49 shows the data from the Enterline and Marsh pre-1947 non-refinery cohort used to estimate the parameters from both the additive and the multiplicative models. The results corresponding to those of the refinery workers above are presented in Table 8-50. The estimate of Δ in the additive model is Δ = 6.055×10^{-8} (additive) with standard error = 2.42×10^{-7}, so that the 95 percent lower and upper bounds are 0 and 4.58×10^{-7}. For the multiplicative model, the estimate of Δ is 3.74×10^{-5} with standard error = 2.23×10^{-4}, so that the 95 percent lower and upper bounds are 0 and 2.60×10^{-4}. These values are used below to estimate incremental unit risks for cancer.

8.3.3.2.1.3 Use of estimates of Δ to estimate unit risk. Mathematically, the risk due to a constant lifetime exposure of x µg/m^3 of nickel in air, in the presence of all other competing risks, may be expressed as

$$P(x) = \int_0^\infty \{h_2(x,t) e^{\int_0^t -[h_2(x,v) + h_1(v)]dv}\} dt$$

TABLE 8-48. EXPECTED LUNG CANCER DEATHS BASED ON THE ADDITIVE AND RELATIVE RISK MODELS AND BOUNDS FITTED TO THE ENTERLINE AND MARSH REFINERY DATA

Exposure interval mg Ni/m^3 months (24-hour/μg/m3 equivalent · years median)		Person-years	Observed	Number of lung cancer deaths predicted under models[a]					
				Additive[b]			Multiplicative[c]		
				Lower bound	MLE	Upper bound	Lower bound	MLE	Upper bound
<10	(76.69)	29.4	0	0.04	0.040	0.041	0.04	0.040	0.041
10-24	(344.93)	223.4	0	0.34	0.347	0.364	0.34	0.347	0.361
25-49	(712.69)	574.2	0	1.00	1.040	1.126	1.00	1.041	1.129
50-99	(1,175.40)	1,858.1	3	3.08	3.291	3.750	3.08	3.286	3.735
100-199	(2,938.22)	335.9	1	0.61	0.711	0.931	0.61	0.712	0.934
≥200	(10,295)	1,460.5	4	2.48	3.933	7.096	2.48	3.935	7.101
		4,481.5	8	7.55	9.36	13.31	7.55	9.36	13.30

[a] No goodness-of-fit tests were calculated because both the expected and the observed are too small.

[b] Predicted = $E_{0j} + \hat{\Delta} X_j W_j$. $\hat{\Delta}_{MLE} = 9.66 \times 10^{-8}$; $\hat{\Delta}_{UCL} = 3.07 \times 10^{-7}$; $\hat{\Delta}_{LCL} = 0$.

Likelihood ratio test for MLE slope: $\chi_1^2 = 0.76$ N.S.

[c] Predicted = $E_{0j}[1 + \hat{\Delta} X_j]$. $\hat{\Delta}_{MLE} = 5.70 \times 10^{-5}$; $\hat{\Delta}_{UCL} = 1.81 \times 10^{-4}$; $\hat{\Delta}_{LCL} = 0$.

Likelihood ratio test for MLE slope: $\chi_1^2 = 0.41$ N.S.

TABLE 8-49. DATA USED TO ESTIMATE Δ AND ITS VARIANCE: ENTERLINE AND MARSH "NON-REFINERY WORKERS" PRE-1947 SUBGROUP

Cumulative exposure (mg Ni/m^3)·mo. (mean worker exposure)	24-hour mg Ni/m3 equivalent x years[a] X_j	Number at risk	Person-years observation W_j	Lung and larynx cancer deaths Expected E_{0j}	Observed O_j	X_jW_j	$X_jW_jO_j$	O_jX_j
4.20	76.69	459	7,993.8	13.22	9	613,044.5	5.5174×10^7	690.21
18.89	344.93	432	7,929.6	13.26	15	2.7352×10^6	4.1027×10^7	5,173.95
39.03	712.69	327	5,918.9	10.35	9	4.2183×10^6	3.7965×10^7	6,414.21
64.37	1,175.40	153	2,404.4	4.43	10	2.8261×10^6	2.8261×10^7	11,754.00
160.91	2,938.22	162	2,981.2	5.35	4	8.7594×10^6	3.8541×10^8	11,752.88
563.80	--	--	None at risk	--	--	--	--	
	5,247.93			46.61	47	1.9152×10^7		

[a] Factor: 1 (mg/m^3) · months = 1 (mg/m^3) · months x 1 year/12 months x 10^3 μg/1 mg x 8/24 x 240/365 = 18.26 (μg/m^3) x years continuous exposure.

[b] $\Sigma E_{0j} \cdot X_j$ = 33,890.45.

Source: Enterline and Marsh (1982).

TABLE 8-50. EXPECTED LUNG CANCER DEATHS BASED ON THE ADDITIVE AND RELATIVE RISK MODELS AND BOUNDS FITTED TO THE ENTERLINE AND MARSH PRE-1947 "NON-REFINERY WORKERS" DATA

Exposure interval mg Ni/m^3 months (24-hour µg/m^3 years--equivalent median)	X_j	Person-years	Observed lung cancer deaths	Number of lung cancer deaths predicted under models					
				Additive[a]			Multiplicative[b]		
				Lower bound	MLE	Upper bound	Lower bound	MLE	Upper bound
<10	(76.69)	7,993.8	9	13.22	13.26	13.50	13.22	13.26	13.48
10-24	(344.93)	7,929.6	15	13.26	13.43	14.51	13.26	13.43	14.45
25-49	(712.69)	5,918.9	9	10.35	10.61	12.28	10.35	10.63	12.27
50-99	(1,175.40)	2,404.4	10	4.43	4.60	5.72	4.43	4.62	5.78
100-199	(2,938.22)	2,981.2	4	5.35	5.88	9.36	5.35	5.94	9.44
	5,247.99	27,227.9	47	46.61	47.78	55.37	46.61	47.87	55.42
X_4^2 goodness-of-fit (Neyman)				5.94	6.27	12.48	5.94	6.31	12.62
p value				N.S.	N.S.	<0.025	N.S.	N.S.	<0.025

[a] Predicted = $E_{0j} + \hat{\Delta}X_jW_j$. $\hat{\Delta}_{MLE} = 6.055 \times 10^{-8}$; $\hat{\Delta}_{UCL} = 4.58 \times 10^{-7}$; $\hat{\Delta}_{LCL} = 0$.

[b] Predicted = $E_{0j}[1 + \hat{\Delta}X_j]$. $\hat{\Delta}_{MLE} = 3.74 \times 10^{-5}$; $\hat{\Delta}_{UCL} = 2.60 \times 10^{-4}$; $\hat{\Delta}_{LCL} = 0$.

where $h_2(x,t)$ is the age-specific death rate at age t due to a constant lifetime exposure at level x, and h(t) is the age-specific death rate for all other causes. The result is derived by Gail (1975). The upper limit ∞ is approximated by the median age of the 1978 U.S. Life Table stationary population. The age-specific "competing causes" rates $h_1(t)$ are also taken from the 1978 U.S. Vital Statistics rates. For the refinery workers, the age-specific death $h_2(x,t)$ are those estimated as

$$h_2(x,t) = 9.66 \cdot 10^{-8}xt$$

for the additive model with the MLE, and

$$h_2(x,t) = h_0(t) \cdot (1 + 5.70 \cdot 10^{-5}xt)$$

for the multiplicative model, with the MLE. The results of the unit risk calculations are presented in Table 8-51, based on the estimates from the Enterline and Marsh refinery cohort, and in Table 8-52 for the Enterline and Marsh non-refinery cohort estimates. The results for the refinery workers (Table 8-51), show, for the additive model, the MLE estimate of the incremental unit risk as 2.8×10^{-4} $(\mu g/m^3)^{-1}$ and the 95 percent upper-limit incremental unit risk as 8.8×10^{-4} $(\mu g/m^3)^{-1}$; for the multiplicative model, the MLE estimate is 1.5×10^{-5} $(\mu g/m^3)^{-1}$ with the 95 percent UCL as 4.7×10^{-5}. For either model computed under the assumptions of 10- or 20-year latent periods, the results change very little. For the non-refinery workers, the estimates are about 30 percent lower than those of the refinery workers under either the additive or the multiplicative model. None of the parameter estimates are statistically significant.

Table 8-51 also presents an estimate of the incremental unit risk under the average relative risk model used by the CAG in cases where there is only one dose-response data point and where the more detailed information, such as person-years and time since first exposure, are not available. This is the same model used below for estimates based on the Clydach and Kristiansand studies. The model is

$$B_H = P_0(R-1)/X$$

TABLE 8-51. ESTIMATED RISKS FOR THE ADDITIVE AND MULTIPLICATIVE MODELS BASED ON THE ENTERLINE AND MARSH REFINERY WORKERS DATA

Model	$\hat{\Delta}$	Incremental risk due to a constant lifetime exposure of 1 μg/m³		
		No lag time	10-year lag time	20-year lag time
Additive risk				
Upper bound	3.07×10^{-7}	8.8×10^{-4}	8.6×10^{-4}	8.2×10^{-4}
MLE	9.66×10^{-8}	2.8×10^{-4}	2.7×10^{-4}	2.6×10^{-4}
Lower bound	0	0	0	0
Relative risk				
Upper bound	1.81×10^{-4}	4.7×10^{-5}	4.2×10^{-5}	3.7×10^{-5}
MLE	5.70×10^{-5}	1.5×10^{-5}	1.3×10^{-5}	1.2×10^{-5}
Lower bound	0	0	0	0
Average relative risk[a]	--	3.1×10^{-5}	--	--

[a] $B_H = P_0\ (R-1)/X$, where $P_0 = 0.023$, $R = 8/7.43$, and $X = 57.4\ \mu g/m^3$ average continuous exposure for a 70-year lifetime.

where B_H = the incremental unit risk estimate; P_0 = the background lifetime risk for lung cancer = 0.036 in the general U.S. white male population (1976)*; R = observed divided by expected lung cancer deaths = 8/7.43 = 1.077 (subtracting expected nasal cancer deaths), and X = average exposure for the refinery cohort on a lifetime continuous exposure basis. For the refinery workers:

$$X = \frac{\Sigma X_j N_j / \Sigma N_j}{70} = 57.4\ \mu g/m^3 \text{ continuous exposure equivalent}$$

(based on the numbers in Table 8-47). The estimate of the incremental unit risk, B_H, is $3.1 \times 10^{-5}\ (\mu g/m^3)^{-1}$, close to the estimate of 1.5×10^{-5} derived

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*This value is adjusted to $P_0 = 0.023$ when the increasing lung mortality rates from 1948 to 1977 are taken into account.

TABLE 8-52. ESTIMATED RISKS FOR THE ADDITIVE AND MULTIPLICATIVE MODELS BASED ON THE ENTERLINE AND MARSH NON-REFINERY WORKERS DATA

		Incremental risk due to a constant lifetime exposure of 1 $\mu g/m^3$		
Model	$\hat{\Delta}$	No lag time	10-year lag time	20-year lag time
Additive				
Upper bound	4.58×10^{-7}	1.3×10^{-3}	1.3×10^{-3}	1.2×10^{-3}
MLE	6.055×10^{-8}	1.8×10^{-4}	1.7×10^{-4}	1.6×10^{-4}
Lower bound	0	0	0	0
Multiplicative				
Upper bound	2.60×10^{-4}	6.6×10^{-5}	6.1×10^{-5}	5.2×10^{-5}
MLE	3.74×10^{-5}	9.5×10^{-6}	8.6×10^{-6}	7.7×10^{-6}
Lower bound	0	0	0	0
Average relative risk	--	2.1×10^{-5}	--	--

above. It is also close to the estimates derived from the Clydach, Wales and Kristiansand, Norway study below.

For the non-refinery workers, the exposures were less than those of the refinery workers. For these non-refinery workers, the average continuous exposure lifetime equivalent was $X = 30.0\ \mu g/m^3$, while $R = 47/45.75$ (subtracting the 0.87 expected nasal cancer deaths) = 1.027. Since $P_0 = 0.036$ as before, the estimate of the incremental unit risk is

$$B_H = \frac{0.023\ (0.027)}{30\ \mu g/m^3} = 2.1 \times 10^{-5}$$

8.3.3.2.2 Copper Cliff, Ontario. Unlike the low exposure/low response of the Huntington refinery, the Copper Cliff refinery was among the dustiest and most hazardous, with relative risks for lung cancer deaths averaging 8.7 (Table 8-39). These data can be analyzed the same way as those of the Huntington refinery workers above, except that only the relative risk model can be fit, since the person-years experience is not available.

In view of the excellent fit to the relative risk model, however, it is most unlikely that a better fit could be established with the excess additive risk model.

In estimating exposure, we refer to Roberts et al. (1984) who stated, "High-volume exhaust-air samples at Copper Cliff indicate airborne nickel sulfide levels of about 400 mg/m^3 in 1950, falling to around 100 mg/m^3 towards the end of the plant's productive life ····." [Public comments by International Nickel Company, Inc., (1986) state that these levels were actually total dust concentrations.] Following, also, the Chovil et al. (1981) organization of data, where they considered early exposure about double that of exposure after 1951, we preserve the estimate of 100 mg/m^3 for the later years, but estimate 200 mg/m^3 as the early exposure. These estimates are also consistent with those of Warner (1985), who reported, from a single 40-hour sample on the floor of the sinter plant, a total dust concentration of 46.4 mg/m^3. An accompanying figure shows estimates of nickel concentrations decreasing from 200 mg/m^3 to 50 mg/m^3 over time.

The results of the analysis are presented in Table 8-53. The maximum likelihood estimate $\hat{\Delta}_{MLE} = 4.19 \times 10^{-5}$ for the relative risk model, with 95 percent limits of $\hat{\Delta}_{LCL} = 2.94 \times 10^{-5}$ and $\hat{\Delta}_{UCL} = 5.44 \times 10^{-5}$, all fit the data satisfactorily. These estimates translate to an incremental unit risk for 1 $\mu g/m^3$ nickel refinery dust exposure of 1.1×10^{-5}, with lower and upper confidence limits of 7.6×10^{-6} and 1.4×10^{-5}. These narrow confidence limits result from the excellent fit by the relative risk model to the data.

For comparison, we fit the data to the average relative risk model. From Table 8-39, it can be seen that

$$R = 8.70;\ X = 100(mg/m^3) \cdot (\Sigma N_j \cdot years_j/\Sigma N_j) \cdot \frac{8}{24} \cdot \frac{280}{365} \cdot \frac{1}{70}$$

$$= 2.24\ mg/m^3 \text{ continuous lifetime equivalent exposure.}$$

Adjusting for the Canadian workers and the rates from 1963 through 1978 yields a value of $P_0 = 0.026$ (see next section).

$$B_H = \frac{0.026(7.7)}{2.24 \times 10^3 \mu g/m^3} = 8.9 \times 10^{-5}$$

TABLE 8-53. DATA ON LUNG CANCER DEATHS USED TO ESTIMATE Δ AND ITS VARIANCE: COPPER CLIFF REFINERY WORKERS (CHOVIL ET AL.) RELATIVE RISK MODEL ONLY

Weighted cumulative exposure (mg/m³)·years[a]	24-hour mg Ni/m³ equivalent · years[b] X_j	Number at risk	Lung cancer deaths			Fit of model[c] with		
			Expected E_{0j}	Observed 0_j	$0_j X_j$	$\hat{\Delta}_{LCL} = 2.95 \times 10^{-5}$	$\hat{\Delta}_{MLE} = 4.19 \times 10^{-5}$	$\hat{\Delta}_{UCL} = 5.44 \times 10^{-5}$
50	10.95	67	0.47	0	0	0.62	0.67	0.75
200	43.80	78	0.36	0	0	0.82	1.02	1.22
400	87.60	82	0.54	3	262.8	1.93	2.52	3.11
650	142.35	77	0.60	4	569.4	3.11	4.18	5.25
950	208.05	70	0.68	6	1248.3	4.84	6.61	8.38
1250	273.75	66	0.76	13	3558.8	6.88	9.48	12.08
1600	350.40	65	0.84	11	3854.4	9.49	13.17	16.85
Total		495	4.25[d]	37		27.74	37.65	47.64
χ_3^2 goodness-of-fit (Neyman) - First four exposures grouped[e]:						3.35	1.72	5.70
p-value						N.S.	N.S.	N.S.

[a] 100 mg/m³ estimated as average after 1952. Before 1952 estimate is 200 mg/m³.

[b] Conversion factor: 1 (mg/m³)· years = 1 (mg/m³)· years x 8/24 x 240/365 = 0.219 (mg/m³)·years continuous exposure.

[c] Units of Δ presented in $(\mu g/m^3)^{-1}$ for comparison with other studies.

[d] $\Sigma E_{0j} \cdot X_j = 797.20$.

[e] First four exposures grouped to provide a valid χ^2 statistic.

Source: Chovil et al. (1981); see also Table 8-39.

The order of magnitude difference in estimates between these two models probably reflects the greater sensitivity of the likelihood model to the lower exposure-response data.

8.3.3.2.3 Kristiansand, Norway. The latest update of this study (Magnus et al., 1982) showed increased but differential risks among different occupational groups, specifically the roasting-smelting and electrolysis workers. Nickel compounds associated with the roasting process include nickel subsulfide, nickel oxide, and nickel dust, while exposure in the electrolysis process includes nickel chloride and nickel sulfate. Exposure estimates for the Kristiansand refinery before 1952 are lacking. All estimates below are based on a review of an analysis by Thornhill (1986). For two of the roasting and smelting operations, Thornhill reports total dust measurements of 5 to 18 mg/m^3 (whole shift samples) in 1952 and 3 to 18 mg/m^3 in 1953 (day shift samples). These are consistent with some earlier measurements, but are slightly higher than several measurements reported later. Thornhill, citing "a steady trend towards improving working conditions following WWII", concludes "that dust levels around the Mond Reducers frequently ranged between 15 and 20 mg/m^3 as estimated by foremen who worked there" (in the early 1950s). If we make minor adjustments based on two assumptions that (1) earlier levels were probably dustier, and (2) The Mond Reducers were among the dustier operations in the process, then a range of 3 to 30 mg/m^3 should provide a reasonable range for which to calculate a unit risk.

For the electrolysis workers, Thornhill estimates that the range of nickel exposures varies from 0.03 to 0.04 mg Ni/m^3 as nickel sulfate for the Copper Electrodispersion tanks (1960, no dust) to 40 mg Ni/m^3 as nickel-copper sulfide and oxide complexes (1974, 80 mg/m^3 total dust). Both the wide range and the nickel species differences seem to preclude a unit risk estimate for these electrolysis workers without individual exposure information. Thus, the calculations that follow are based on the roasting and smelting operations.

The study did not record the number of years worked; therefore, it is assumed that exposure lasted for about one quarter of a lifetime. The meager evidence suggests that this may be a slight overestimate. The corresponding estimate for Clydach was 10.5 years before 1930, when exposure to the carcinogen was drastically reduced. In Norway, there is no corresponding cutoff date.

For the low end of the exposure range, we can estimate an average lifetime exposure for workers as

$$\text{exposure} = 3\ \text{mg/m}^3 \times \frac{8}{24}\ \text{hours} \times \frac{240}{365}\ \text{days} \times \frac{1}{4}\ \text{lifetime} \times 10^3\ \mu\text{g/mg}$$

$$= 164\ \mu\text{g/m}^3$$

For the high end of the range, average lifetime exposure is 1644 $\mu g/m^3$.

The estimated incremental unit risk, B_H, of dying from cancer due to exposure to these airborne nickel compounds at 1 $\mu g/m^3$ over 70 years of continuous exposure is given by

$$B_H = P_0(R - 1)/X$$

The relative risk, R, for roasting and smelting workers in the 1982 update was 3.9 for lung and larynx cancer. The background lung cancer risk for Norwegian males, P_0, has been estimated as approximately 45 percent that of the U.S. white males based on 1976-77 age-adjusted death rates (Page et al., 1985), or 0.016. This is consistent with the figures of Warner (1986) for Norwegian males, if we accept the background rates of 1976 as valid figures for comparison. If we consider that the U.S. age-adjusted death rates for lung cancer rose from 25.9 in 1953 (the first year of the study; Grove, 1968) to 68.1 in 1976, and attribute a similar trend to the Norwegian population, then the background rate of $P_0 = 0.011$ applies.

The incremental unit risk of death from lung and larynx cancer from nickel per increment of 1 $\mu g/m^3$ of continuous exposure for 70 years is estimated as:

$$B_H = 0.011(2.9)/164 = 1.9 \times 10^{-4}\ (\mu g/m^3)^{-1}$$

based on the low exposure estimate of 3 mg/m^3

and

$$B_H = 1.9 \times 10^{-5}\ (\mu g/m^3)^{-1}$$

based on the high exposure estimate of 30 mg/m^3.

8.3.3.2.4 Clydach, Wales. A risk assessment can also be made from the epidemiologic data at Clydach, Wales (Doll et al., 1977). The lung cancer rates prior to 1930 will be used to calculate the risk, because the observed cancer risk declined dramatically after 1925; this reduction in risk was statistically significant after 1930. As discussed in the epidemiology section, it is believed that the refining procedure used after 1925 led to the carcinogen being drastically reduced in the environment. INCO estimates that prior to 1930, the concentration of airborne nickel dust in areas of high exposure was 20 mg to 50 mg Ni/m^3. Morgan (1985) estimated that exposure in 1932 ranged from approximately 8 to 42 mg/m^3 during a period when the plant was operating below capacity. Because not all workers were in high risk areas, and those who were probably were exposed for less than 8 hours/day, we estimate 10 mg Ni/m^3 as the lower bound to the range.

Because the exposure estimate used describes conditions between 1900 and 1930 only, the fraction of lifetime exposed should reflect exposure before 1930 only. This can be estimated as shown in Table 8-54.

Average number of years exposed is 8,032.5/762 = 10.5 years, or 0.15 of a 70-year lifetime.

The average lifetime exposure for the workers, X, was:

$$X = 10\ \text{mg/m}^3 \times \frac{8}{24}\ \text{hours} \times \frac{240}{365}\ \text{days} \times 0.15\ \text{lifetime} \times 10^3\ \mu\text{g/mg}$$

$$= 329\ \mu\text{g/m}^3 \text{ for the low exposure estimate and}$$

$$X = 1{,}644\ \mu\text{g/m}^3 \text{ for the high-exposure estimate.}$$

The relative risk estimated by Doll was 6.2 for lung cancer (ICD 161-163). The lifetime lung cancer risk, P_0, adjusted to the population of England and Wales from 1934 to 1977, is approximately 0.029.

The range of estimated incremental risk of death from lung cancer from nickel at the rate of 1 µg/m^3 for 70 years of continuous exposure is:

$$B_H = \frac{(0.029)\ (5.2)}{329\ \mu\text{g/m}^3} = 4.6 \times 10^{-4} (\mu\text{g/m}^3)^{-1}$$

for the low exposure limit and

$$B_H = 8.1 \times 10^{-5}\ (\mu\text{g/m}^3)^{-1} \text{ for the high exposure limit.}$$

TABLE 8-54. ESTIMATION OF FRACTION OF LIFETIME EXPOSED TO NICKEL IN THE WORKPLACE, CLYDACH, WALES

Period starting employment	Number of men	x	Average number of years exposed prior to 1930	=	Person-years exposed
1902-1909	119	x	25		2975
1910-1914	150	x	17.5		1875
1915-1919	105	x	12.5		787.5
1920-1924	285	x	7.5		2137.5
1925-1929	103	x	2.5		257.5
Total	762		2.5		8032.5

Source: Adapted from Doll et al. (1977).

8.3.3.2.5 Conclusion and discussion: Recommended unit risk estimates based on human studies. The results of the analyses from the various models and human data sets are presented in Table 8-55. The estimates for the refinery workers range from 1.1 x 10^{-5} to 4.6 x 10^{-4}. The estimates from the Huntington refinery are somewhat lower, but this may be merely a result of the small sample size. We note that if the two nasal cancer deaths are added to the eight lung cancer deaths, the incremental unit-risk estimate becomes 1.3 x 10^{-4}, well within the range of the other estimates. If a more specific estimate is needed, we recommend the midpoint of the range, 2.4 x 10^{-4}. This is very close to the estimate derived from the additive risk model for the Huntington refinery workers.

For the Huntington non-refinery workers, the MLE estimates are about 30 percent less than those of the Huntington refinery workers, regardless of which model is used, but neither of these estimates is statistically significant. In fact, an incremental risk estimate of zero fits the data (by the χ^2 goodness-of-fit) as well as the MLE estimate for either model. This is consistent with the qualitative finding of no data supporting an excess risk for the non-refinery nickel workers. On the other hand, we cannot say that these non-refinery data support a zero increased risk either, since the estimates are also consistent with those from the refinery workers.

TABLE 8-55. ESTIMATES OF INCREMENTAL UNIT RISKS FOR LUNG CANCER DUE TO EXPOSURE TO 1 μg Ni/m^3 FOR A LIFETIME BASED ON EXTRAPOLATIONS FROM EPIDEMIOLOGIC DATA SETS

Study	Additive risk model	Relative risk model
Huntington, W. Va.[a]		
Refinery workers	2.8×10^{-4}	1.5×10^{-5} - 3.1×10^{-5}[b,c]
Non-refinery workers	1.8×10^{-4}	9.5×10^{-6} - 2.1×10^{-5}[c]
Copper Cliff, Ontario	--	1.1×10^{-5} - 8.9×10^{-5}[c]
Clydach, Wales	--	8.1×10^{-5} - 4.6×10^{-4}
Kristiansand, Norway	--	1.9×10^{-5} - 1.9×10^{-4}
Midpoint of range for refinery workers	2.4×10^{-4}	

[a] MLE estimates only.

[b] Incremental unit risk increases to 1.3×10^{-4} if the two observed nasal cancer deaths and expected nasal cancer deaths are included.

[c] Average relative risk model.

We conclude that:

(1) For the refinery workers exposed to refinery dust, an incremental unit risk of

$$B_H = 2.4 \times 10^{-4} \ (\mu g/m^3)^{-1}$$

is consistent with results from the four data sets.

Since nickel subsulfide is a major component of the refinery dust and nickel subsulfide has been shown to be the most carcinogenic nickel compound in animals (supported by in vitro studies), this incremental unit risk estimate might be used for nickel subsulfide with a multiplication factor of 2 to account for the roughly 50 percent nickel subsulfide composition. While nickel oxide and nickel sulfate are two other important nickel compounds in the refinery dust, their possible carcinogenic potencies relative to the subsulfide have not been established and the above estimate cannot be used for either the oxide or the sulfate form.

(2) For the non-refinery workers, those not exposed to nickel subsulfide, we are unable to estimate an incremental unit risk. The low exposure/low re-

sponse of these non-refinery workers do not provide a sufficient data base to support a quantitative estimate of the carcinogenicity of these compounds. The wide range of quantitative estimates, including zero, reflects this uncertainty.

8.3.4 Relative Potency

One of the uses of the concept of unit risk is to compare the potency of carcinogens. To estimate the relative potency on a per mole basis, the unit risk slope factor is multiplied by the molecular weight and the resulting number expressed in terms of $(\text{mmol/kg/day})^{-1}$. This is called the relative potency index.

Figure 8-6 is a histogram representing the frequency distribution of the potency indices of 55 chemicals evaluated by the CAG as suspected carcinogens. The actual data summarized by the histogram are presented in Table 8-56. Where human data are available for a compound, they have been used to calculate the index. Where no human data are available, animal oral studies and animal inhalation studies have been used in that order. Animal oral studies are selected over animal inhalation studies because animal oral studies have been conducted on most of these chemicals; this allows potency comparisons by route.

The potency index for nickel refinery dust based on lung cancer in occupational studies of nickel refinery workers is $2.5 \times 10^{+2}$. This is derived as follows: the range of unit risk estimates based on both additive and relative risk models is 1.1×10^{-5} - 4.6×10^{-4} $(\mu g/m^3)^{-1}$ (Table 8-54). We first take the midpoint of the range 2.4×10^{-4} $(mg/m^3)^{-1}$. This is converted to units of $(\text{mg/kg/day})^{-1}$, assuming a breathing rate of 20 m^3 of air per day and 70 kg person.

$$2.4 \times 10^{-4}\ (\mu g/m^3)^{-1} \times \frac{1\ \text{day}}{20\ m^3} \times \frac{1\ \mu g}{10^3\ \mu g/mg} \times 70\ \text{kg} = 0.84\ (\text{mg/kg/day})^{-1}$$

For current purposes, we multiply this estimate by 240.25, the molecular weight of nickel subsulfide, the principal component of nickel refinery dust. Multiplying by the molecular weight of 240.25 gives a potency index of $2.0 \times 10^{+2}$. Rounding off to the nearest order of magnitude gives a value of +2, which is the scale presented on the horizontal axis of Figure 8-6. The index of $2.0 \times 10^{+2}$ lies in the third quartile of the 55 substances that the CAG has evaluated as suspect carcinogens. For nickel subsulfide the estimate of potency is adjusted by a factor of 2, giving a potency index of $4 \times 10^{+2}$.

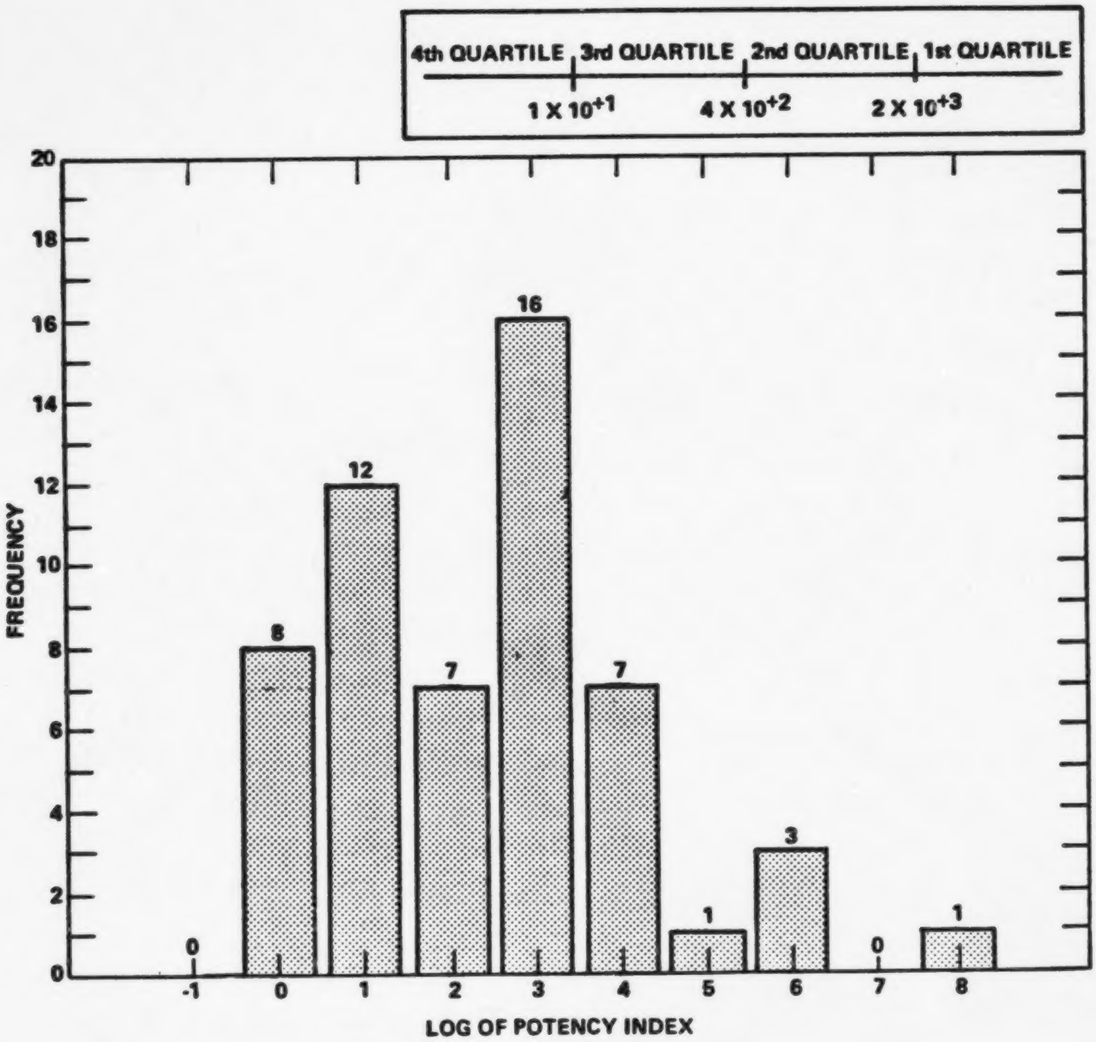

Figure 8-6. Histogram representing the frequency distribution of the potency indices of 55 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 8-56. RELATIVE CARCINOGENIC POTENCIES AMONG 55 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS

Compounds	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
Acrylonitrile	107-13-1	L	S	2A	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	1162-65-8	L	S	2A	2900	312.3	$9x10^{+5}$	+6
Aldrin	309-00-2	I	L	3	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride	107-05-1				$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	7440-38-2	S	I	1	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	50-32-8	I	S	2B	11.5	252.3	$3x10^{+3}$	+3
Benzene	71-43-2	S	S	1	$2.9x10^{-2}$(W)	78	$2x10^{0}$	0
Benzidene	92-87-5	S	S	1	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	7440-41-7	L	S	2A	2.6(W)	9	$2x10^{+1}$	+1
1,3-Butadiene	106-99-0	I	S	2B	$1.0x10^{-1}$(I)	54.1	$5x10^{0}$	+1
Cadmium	7440-43-9	L	S	2A	6.1(W)	112.4	$7x10^{+2}$	+3
Carbon tetrachloride	56-23-5	I	S	2B	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	57-74-9	I	L	3	1.61	409.8	$7x10^{+2}$	+3

(continued on the following page)

TABLE 8-56. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude ($\log_{10}$ index)
Chlorinated ethanes								
1,2-Dichloroethane (Ethylene dichloride)	107-06-2	I	S	2B	$9.1x10^{-2}$	98.9	$9x10^{0}$	+1
Hexachloroethane	67-72-1	I	L	3	$1.42x10^{-2}$	236.7	$3x10^{0}$	0
1,1,2,2-Tetrachloroethane	79-34-5	I	L	3	0.20	167.9	$3x10^{+1}$	+1
1,1,2-Trichloroethane	79-00-5	I	L	3	$5.73x10^{-2}$	133.4	$8x10^{0}$	+1
Chloroform	67-66-3	I	S	2B	$7x10^{-2}$	119.4	$8x10^{0}$	+1
Chromium VI	7440-47-3	S	S	1	41(W)	100	$4x10^{+3}$	+4
DDT	50-29-3	I	S	2B	0.34	354.5	$1x10^{+2}$	+2
Dichlorobenzidine	91-94-1	I	S	2B	1.69	253.1	$4x10^{+2}$	+3
1,1-Dichloroethylene (Vinylidene chloride)	75-35-4	I	L	3	1.16(I)	97	$1x10^{+2}$	+2
Dichloromethane (Methylene chloride)	75-09-2	I	S	2B	$1.4x10^{-2}$(I)	84.9	$1x10^{0}$	0
Dieldrin	60-57-1	I	S	2B	30.4	380.9	$1x10^{+4}$	+4
2,4-Dinitrotoluene	121-14-2	I	S	2B	0.31	182	$6x10^{+1}$	+2
Diphenlhydrazine	122-66-7	I	S	2B	0.77	180	$1x10^{+2}$	+2
Epichlorohydrin	106-89-8	I	S	2B	$9.9x10^{-3}$	92.5	$9x10^{-1}$	0
Bis(2-chloroethyl)ether	111-44-4	I	S	2B	1.14	143	$2x10^{+2}$	+2

(continued on the following page)

TABLE 8-56. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
Bis(chloromethyl)ether	542-88-1	S	S	1	9300(I)	115	$1x10^{+6}$	+6
Ethylene dibromide (EDB)	106-93-4	I	S	2B	41	187.9	$8x10^{+3}$	+4
Ethylene oxide	75-21-8	L	S	2A	$3.5x10^{-1}$(I)	44.1	$2x10^{+1}$	+1
Heptachlor	76-44-8	I	S	2B	3.37	373.3	$1x10^{+3}$	+3
Hexachlorobenzene	118-74-1	I	S	2B	1.67	284.4	$5x10^{+2}$	+3
Hexachlorobutadiene	87-68-3	I	L	3	$7.75x10^{-2}$	261	$2x10^{+1}$	+1
Hexachlorocyclohexane technical grade								
alpha isomer	319-84-6	I	S	2B	4.75	290.9	$1x10^{+3}$	+3
beta isomer	319-85-7	I	L	3	11.12	290.9	$3x10^{+3}$	+3
gamma isomer	58-89-9	I	L	3	1.84	290.9	$5x10^{+2}$	+3
					1.33	290.9	$4x10^{+2}$	+3
Hexachlorodibenzo-dioxin	34465-46-8	I	S	2B	$6.2x10^{+3}$	391	$2x10^{+6}$	+6
Nickel refinery dust		S	S	1	0.84(W)	240.2	$2x10^{+2}$	+2
Nickel subsulfide	0120-35-722	S	S	1	1.7(W)	240.2	$4x10^{+2}$	+3
Nitrosamines								
Dimethylnitrosamine	62-75-9	I	S	2B	25.9(not by q_1^*)	74.1	$2x10^{+3}$	+3
Diethylnitrosamine	55-18-5	I	S	2B	43.5(not by q_1)	102.1	$4x10^{+3}$	+4
Dibutylnitrosamine	924-16-3	I	S	2B	5.43	158.2	$9x10^{+2}$	+3

(continued on the following page)

TABLE 8-56. (continued)

Compounds	CAS Number	Level of evidence[a]		Grouping based on IARC criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
N-nitrosopyrrolidine	930-55-2	I	S	2B	2.13	100.2	$2x10^{+2}$	+2
N-nitroso-N-ethylurea	759-73-9	I	S	2B	32.9	117.1	$4x10^{+3}$	+4
N-nitroso-dimethylurea	684-93-5	I	S	2B	302.6	103.1	$3x10^{+4}$	+4
N-nitroso-diphenylamine	86-30-6	I	S	2B	$4.92x10^{-3}$	198	$1x10^{0}$	0
PCBs	1336-36-3	I	S	2B	4.34	324	$1x10^{+3}$	+3
Phenols 2,4,6-Trichlorophenol	88-06-2	I	S	2B	$1.99x10^{-2}$	197.4	$4x10^{0}$	+1
Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	I	S	2B	$1.56x10^{+5}$	322	$5x10^{+7}$	+8
Tetrachloroethylene	127-18-4	I	L	3	$5.1x10^{-2}$	165.8	$8x10^{0}$	+1
Toxaphene	8001-35-2	I	S	2B	1.13	414	$5x10^{+2}$	+3
Trichloroethylene	79-01-6	I	L/S	3/2B	$1.1x10^{-2}$	131.4	$1x10^{0}$	0
Vinyl chloride	75-01-4	S	S	1	$1.75x10^{-2}$(I)	62.5	$1x10^{0}$	0

[a] S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

[b] Animal slopes are 95% upper-bound slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), Δ (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear nonthreshold model. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available. The slope value is an upper bound in the sense that the true value (which is unknown) is not likely to exceed the upper bound and may be much lower, with a lower bound approaching zero. Thus, the use of the slope estimate in risk evaluations requires an appreciation for the implications of the upper bound concept as well as the "weight of evidence" for the likelihood that the substance is a human carcinogen.

[c] The potency index is a rounded-off slope in $(mmol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

Ranking of the relative potency indices is subject to the uncertainty of comparing potency estimates for a number of chemicals based on different routes of exposure in different species using studies whose quality varies widely. Furthermore, all of the indices are based on estimates of low-dose risk using linear extrapolation from the observational range. Thus, these indices are not valid to compare potencies in the experimental or observational range if linearity does not exist there. Finally, the index for nickel refinery dust is subject to the additional uncertainty of not being able to accurately quantify the potencies of the specific nickel carcinogens in the refinery other than nickel subsulfide.

8.4 SUMMARY

8.4.1 Qualitative Analysis

Nickel, at least in some forms, should be considered carcinogenic to humans when inhaled. Evidence of a cancer risk is strongest in the sulfide nickel matte refining industry. This evidence includes a consistency of findings across different studies in different countries, specificity of tumor site (lung and nose), high relative risks, particularly for nasal cancer, and a dose-response relationship by length of exposure. There are also animal and *in vitro* studies on nickel compounds which support the concern that at least some forms of nickel should be considered carcinogenic. The animal studies employed mainly injection as the route of exposure, with some studies using inhalation as the exposure route. While the majority of the compounds tested in the injection studies caused tumors at the injection site only, nickel acetate, when tested in Strain A mice, and nickel carbonyl, at toxic levels, have also caused distal site primary tumors. The relevance of injection site only tumors in animals to human carcinogenic hazard via inhalation, ingestion, or cutaneous exposure is uncertain. Thus, the bulk of the evidence from injection studies on different nickel compounds, which is summarized in the following sections, constitutes only limited evidence for carcinogenicity. Three low-dose drinking water studies and one diet study with soluble nickel compounds have not shown any increase in tumors of the dosed animals.

It is possible that it is the nickel ion that is carcinogenic once inside the cell, and that potential differences in carcinogenic activity of different nickel compounds are a function of the particular nickel compound's ability to enter the cell. Following this hypothesis, experiments have been conducted to correlate carcinogenicity via injection with physical, chemical, and biological activities. While it is suggested from such studies that, on a qualitative basis, some nickel compounds may have higher carcinogenic potential than others, the relationships between physical, chemical, and biological indices are not currently well enough established to allow a quantitative comparison. Following the reasoning that there may be differences among nickel compounds with regard to carcinogenic potency, the following summaries present the qualitative evidence for the most-studied nickel compounds or mixtures of compounds.

8.4.1.1 Nickel Subsulfide (Ni_3S_2). The evidence for carcinogenicity among the different nickel compounds is strongest for nickel subsulfide. Workers in the areas of refineries where nickel subsulfide is believed to have constituted most of the nickel exposure have increased risks of cancers of the nasal cavity and lung. Nickel subsulfide has also been shown to be carcinogenic by numerous routes of administration in several animal species and strains. The observation of adenomas and adenocarcinomas in rats exposed to nickel subsulfide by inhalation and when injected into heterotopic trachea grafts supports the concern of human carcinogenicity when nickel subsulfide is inhaled.

The observation of injection-site sarcomas from the various studies on several species of animals, the induction of morphological transformations of mammalian cells in culture, the induction of sister chromatid exchanges, the inhibition of DNA synthesis, the induction of DNA strand breaks, and the observation of nickel concentrating in the cell nucleus all further support the carcinogenicity of nickel subsulfide. Furthermore, in terms of potency, nickel subsulfide has been shown to be either the most potent or among the most potent of the nickel compounds in all of the comparative tests.

8.4.1.2 Nickel Refinery Dust. Based on large excesses of lung and nasal cancer in several epidemiologic studies in different countries, including strong exposure response relationships, nickel refinery dust from pyrometallurgical sulfide nickel matte refineries can be classified as a known human carcinogen. The excess risks are greatest in the dustier parts of the refinery (e.g., calcining and sintering). Nickel compounds in the dustier areas include nickel subsulfide, nickel sulfate, and nickel oxide.

Nickel refinery dust also has been studied for potential carcinogenicity in animals. Nickel refinery flue dust containing 68 percent nickel subsulfide, 20 percent nickel sulfate, and 6.3 percent nickel oxide gave either negative or equivocal results from inhalation studies in rats. However, intramuscular injections produced strong tumor responses in both rats and mice. The observation of pulmonary squamous cell carcinomas in two of five surviving rats that were exposed by inhalation to feinstein dust (an intermediate product of nickel refining containing NiS, NiO, and metallic nickel) further supports nickel refinery dust as a potential human carcinogen. These dusts have not been studied using *in vitro* short-term test systems or tests for macromolecular interactions.

8.4.1.3 Nickel Carbonyl [$Ni(CO)_4$]. Nickel carbonyl was the first nickel compound suspected of causing cancer in humans. Detailed analysis of the epidemiologic data from a study of workers at the sulfide nickel matte refinery at Clydach, Wales, however, did not find that workers in the reduction area, where nickel carbonyl exposure was present, had an excess risk of cancer. With respect to animals, however, nickel carbonyl administered to rats via inhalation produced pulmonary adenocarcinomas, and intravenous injections into rats gave malignant tumors at various sites. Biochemical studies have shown that the nickel from nickel carbonyl is bound to DNA and inhibits RNA polymerase activities. The data taken together provide sufficient evidence that nickel carbonyl is an animal carcinogen and should be considered a probable human carcinogen.

8.4.1.4 Nickel Oxide (NiO). The evidence for the carcinogenic potential of nickel oxide is equivocal and, in general, the study designs have been inadequate for the determination of carcinogenicity specific to nickel oxide. With regard to epidemiologic studies, nickel oxide generally occurred as one component of the refinery dust in the very dusty calcining and sintering areas of pyrometallurgical sulfide nickel matte refineries where the lung and nasal cancer risks were high. Yet in other occupational settings, such as nickel alloy manufacturing and nickel oxide ore refining, where nickel oxide exposure was believed to occur without nickel subsulfide exposure, increased cancer risks were not found. This latter finding, however, may be simply a function of the intensity of nickel exposure, as these latter occupational settings were far less dusty than the nickel matte refineries. Exact comparisons of the ambient levels of nickel in these dustier areas with ambient levels of nickel in occupational settings where nickel oxide, nickel dust, or nickel compounds other than the subsulfide are believed to be the primary exposure are difficult because of possible improvements in industrial hygiene prior to the time when the measurements were taken and because of presumed differences in sampling techniques.

In animals, while nickel oxide was carcinogenic in five intramuscular injection studies and one intrapleural injection study, it produced only injection site tumors. The response by the intrapleural route, however, was strong and approached the response produced by nickel subsulfide. The results of one inhalation study with Syrian golden hamsters, a strain resistant to lung tumors, showed neither a carcinogenic effect alone nor a co-carcinogenic effect with cigarette smoke. An inhalation study with rats was inconclusive. Responses from the various intramuscular injection studies varied depending on the dose and animal species and strains used. To the extent that injection studies can be used to compare carcinogenic potency, the injection site tumor results indicate that nickel oxide is most likely less carcinogenic than nickel subsulfide. Cell transformation assays give equivocal results: negative with SHE cells and positive with BHK-21 cells with an activity about one tenth of that of nickel subsulfide.

8.4.1.5 Nickelic Oxide (Ni_2O_3). Nickel (III) oxide (Ni_2O_3) has neither been evaluated in human studies, nor been tested sufficiently in animal studies to allow any definite conclusions to be drawn about its carcinogenic potential. In animals, nickelic oxide gave a marginal tumor response by intracerebral injection, but intramuscular injections of the same animals produced no injection-site sarcomas. It produced no tumors in a second intramuscular injection study. However, nickelic oxide is more active in the induction of morphological transformations of mammalian cells in culture than is nickel oxide. The transforming activity in BHK-21 cells approximates that of nickel subsulfide but in SHE cells it shows only about one tenth the activity of nickel subsulfide.

8.4.1.6 Soluble Nickel Compounds [$NiSO_4$, $NiCl_2$, $Ni(CH_3COO)_2$]. The evidence for three soluble nickel compounds, nickel sulfate ($NiSO_4$), nickel chloride ($NiCl_2$), and nickel acetate [$Ni(CH_3COO)_2$], is summarized here as a class both because of hypothesized similar modes of action of the soluble compounds and because of limited testing of the different compounds. The results from four intramuscular injection studies and one ingestion study on nickel sulfate were negative. Two low-dose drinking water studies with nickel acetate and one low-dose diet study with nickel sulfate were also negative. The only study on nickel chloride was an intramuscular implantation study, which gave negative results. Both the sulfate and the chloride, however, induce morphological transformations of mammalian cells in culture, sister chromatid exchange, chromosomal aberrations *in vitro*, gene mutations in yeast, and mammalian cells in culture, and decrease fidelity of DNA synthesis. The observation of pulmonary tumors in strain A mice from the administration of nickel acetate by intraperitoneal injections and the ability of nickel acetate to transform mammalian cells in culture and to inhibit RNA and DNA synthesis provides limited evidence for the carcinogenicity of nickel acetate and supports a concern for the carcinogenic potential of other soluble nickel compounds. However, testing of these soluble nickel compounds is too limited to support any definitive judgment regarding their carcinogenic potential.

With respect to humans, the evidence is somewhat contradictory and must be examined carefully. Electrolysis workers at the refinery in Kristiansand, Norway experienced the highest lung cancer risk in the refinery. Nickel exposures in the electrolysis area were predominantly to nickel chloride and nickel sulfate, both soluble nickel salts, but there is also a report of heavy exposure to the less soluble forms. Other nickel exposures may also have occurred, however, due to the proximity of the electrolysis process to other parts of the plant and because of the removal of impure nickel waste from the electrolysis cells by the electrolysis workers. Lung cancer risk was not found among electrolysis workers at Port Colborne, Ontario, but it is possible that there were qualitative and quantitative differences in exposure between the electrolysis workers at Port Colborne and those at Kristiansand.

8.4.1.7 Nickel Sulfide (NiS). Significantly elevated mortality from pancreatic and prostate cancer was found among 30,000 nickel workers employed by INCO in the Sudbury region of Ontario. These workers had mining but no sinter plant or office experience. In the mines, the workers were reported to be exposed to nickel/iron sulfide, not exposed to asbestos, and exposed to only low levels of radon daughters. It was not indicated what other exposures may have been present. Both pancreatic and prostate cancer mortality showed a dose-response by duration of employment.

Elevated lung and laryngeal cancer was found among a different group of nickel workers with mining experience who also worked in the Sudbury region of Ontario but were employed by Falconbridge, Ltd. Presumably, this group of workers had similar exposures to those of the INCO workers; however, the Falconbridge workers included individuals who had sinter plant experience which may have produced the elevations in lung and laryngeal cancer mortality.

The individual results from these two studies provide some suggestions that the nickel mining occupation and perhaps nickel sulfide exposure are associated with an excess risk of cancer. This suggestion of an increased risk is weakened, however, by the lack of consistency in tumor site mortality between the two studies, the inclusion of workers as miners, in both studies, who had occupational experience other than nickel mining, and the lack of complete exposure data for the mining operations. As a result, the human evidence for an association of nickel sulfide or the mining occupation with excess cancer risk is considered inadequate.

In animals, crystalline nickel sulfide has been found to be a potent carcinogen by the intramuscular and intrarenal injection routes of exposure. Its carcinogenic activity equals that of nickel subsulfide by the intramuscular route and is more active than nickel subsulfied by the intrarenal route. It also induces morphological transformations of mammalian cells in culture with an activity equal to that of nickel subsulfide. In the same sets of experiments, however, amorphous nickel sulfide was inactive both as an animal carcinogen by the intramuscular or intrarenal injection routes of exposure and in the induction of morphological transformations of mammalian cells in culture.

X-ray powder diffraction of insoluble crystalline material present in the tumors of Ni_3S_2-injected mice indicated that a conversion of Ni_3S_2 to Ni_7S_6 and NiS had occurred. The conversion of nickel subsulfide to nickel sulfide and other nickel sulfide forms heightens the concern for the carcinogenicity of nickel sulfide.

In summary, the evidence from animals for the carcinogenicity of crystalline nickel sulfide is limited. There is no evidence that amorphous nickel sulfide is carcinogenic.

8.4.1.8 Nickel Metal (Ni). In most of the epidemiologic studies where there was believed to be exposure to nickel metal, statistically significant excess cancer risks were not found. In studies of workers believed to be exposed to metallic nickel dust where significant excess risks were found (e.g., nickel/chromium alloy manufacturing and nickel/cadmium battery workers), there was concurrent exposure to other known or suspected lung carcinogens which confound the results.

In animals, nickel metal, in the form of dust or pellets, leads to the induction of malignant sarcomas at the site of injection in rats, rabbits, and possibly hamsters. However, the few inhalation studies on metallic nickel have not shown that it produces lung tumors. Based on the strong tumor response from intramuscular injection studies, the observation of adenomatoid lesions of the respiratory tract from inhalation studies, and the ability of powdered nickel to induce morphological transformation of mammalian cells in culture, metallic nickel should be considered to have limited animal evidence for carcinogenicity.

8.4.2 Quantitative Analysis

The results of the analysis of lung cancer data in four sulfide ore nickel refineries suggest a range of carcinogenic potency for nickel matte refinery dust in workers of 1.1×10^{-5} to 4.6×10^{-4} $(\mu g\ Ni/m^3)^{-1}$. As a best estimate, we take the midpoint of the range, 2.4×10^{-4} $(\mu g\ Ni/m^3)^{-1}$ as the incremental unit risk due to a lifetime exposure to nickel matte refinery dust. Since the major component in this refinery dust is nickel subsulfide, which has been shown to be the most carcinogenic nickel compound in animals (supported by in vitro studies), this incremental unit risk might also be used for extrapolating risks due to nickel subsulfide exposure. If this is done, increasing the unit risk by a factor of 2 to adjust for the approximately 50 percent nickel subsulfide in the refinery dust is appropriate. For nickel oxide and nickel sulfate, two other important nickel compounds in the refinery dust, their possible carcinogenic potencies relative to the subsulfide have not been established and the above unit risk estimate cannot be used for either the oxide or the sulfate form.

Upper-limit incremental unit risks for nickel subsulfide exposure have also been estimated from a rat inhalation study. They range from $q_1^* = 2.7 \times 10^{-3}$ to 6.1×10^{3} $(\mu g/m^3)^{-1}$, with maximum likelihood estimates ranging from 1.8×10^{-3} to 4.1×10^{-3} $(\mu g/m^3)^{-1}$. The estimate based on subsulfide exposure to human refinery workers is about one-seventh of these estimates. The lower estimate based on human studies is recommended for a quantitative extrapolation.

For the non-refinery workers, those not exposed to nickel subsulfide, we are unable to estimate an incremental unit risk. The low exposure/low response of these non-refinery workers do not provide a data base sufficient for a quantitative estimate. The animal data base of relative carcinogenic activities of the various nickel compounds is also not sufficient to estimate a quantitative potency of these compounds relative to either nickel subsulfide or nickel refinery dust.

8.5 CONCLUSIONS

There are only three compounds or mixtures of nickel compounds which can currently be classified as either Group A or B, according to the Environmental

Protection Agency's classification scheme for evaluating carcinogens (U.S. Environmental Protection Agency, 1984). Nickel refinery dust from pyrometallurgical sulfide nickel matte refineries is classified as Group A. Nickel subsulfide is believed to be the major nickel component of this refinery dust. This, along with the evidence from animal studies on nickel subsulfide, is sufficient to conclude that nickel subsulfide is also in Group A. While there is inadequate evidence from epidemiologic studies with regard to evaluating the carcinogenicity of nickel carbonyl, there is sufficient evidence from animal studies to classify it as Group B2. The carcinogenic potential of other nickel compounds remains an important area for further investigation. Some biochemical and *in vitro* toxicological studies seem to indicate the nickel ion as a potential carcinogenic form of nickel and nickel compounds. If this is true, all nickel compounds might be potentially carcinogenic, with potency differences related to their ability to enter and make the carcinogenic form of nickel available to a susceptible cell. However, at the present time neither the bioavailability nor the carcinogenesis mechanism of nickel compounds is well understood.

Estimates of carcinogenic risk to humans from exposure via inhalation of nickel refinery dust and nickel subsulfide have been calculated from cancer epidemiologic studies. The quantitative incremental unit risk for nickel refinery dust is 2.4×10^{-4} $(\mu g/m^3)^{-1}$; the quantitative unit risk estimate for nickel subsulfide is twice that for nickel refinery dust. Comparing the potency of nickel subsulfide to 55 other compounds that the Environmental Protection Agency has evaluated as suspect or known human carcinogens, nickel subsulfide would rank between the second and third quartiles.

8.6 REFERENCES

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9. NICKEL AS AN ESSENTIAL ELEMENT

Nickel has been established as an essential element in prokaryotic organisms and experimental animals, and there is suggestive evidence that the element may also play an essential role in humans (National Academy of Sciences, 1975; Thomson, 1982; Nielsen, 1980).

Mertz (1970) has established criteria for essentiality of trace elements as micronutrients, and this discussion will focus primarily on one of the most critical of these: demonstration of specific deficiency-related syndromes which are prevented or cured by the element alone.

Earlier studies in trace-element nutritional research could not demonstrate any consistent effects of nickel deficiency (Spears and Hatfield, 1977; National Academy of Sciences, 1975), owing in part to the technical difficulties of controlling nickel intake because of its ubiquity. Later studies demonstrated adverse effects of nickel deprivation in various animal models, including chicks, cows, goats, minipigs, rats, and sheep.

Nielsen and Higgs (1971) showed a nickel-deficiency syndrome in chicks fed nickel at levels of 40 to 80 ppb (control diet: 3 to 5 ppm) characterized by swollen hock joints, scaly dermatitis of the legs, and fat-depleted livers. Sunderman et al. (1972) observed ultrastructural lesions such as perimitochondrial dilation of rough endoplasmic reticulum in hepatocytes of chicks fed a diet having 44 ppb nickel. Nielsen and Ollerich (1974) also noted hepatic abnormalities similar to those reported by Sunderman et al. (1972).

Growth responses to nickel supplementation have been reported for rats (Nielsen et al., 1975; Schnegg and Kirchgessner, 1975a; Schroeder et al., 1974) and pigs (Spears, 1984; Spears et al., 1984; Anke et al., 1974). Rats maintained on nickel-deficient diets through three successive generations showed a 16 percent and 26 percent weight loss in the first and second generations, respectively, when compared to nickel-supplemented controls (Schnegg and Kirchgessner, 1975a). Pigs fed a diet containing 100 ppb nickel also showed signs of decreased growth rate. However, body weight gain was not affected in neonatal pigs fed supplemental concentrations of 5 and 25 ppm nickel ($NiCl_2$) in milk-based diets (Spears et al., 1984). Spears and co-workers noted that the discrepancy between their study and that of others may have been due to the higher nickel content (0.12 and 0.16 ppm) in the basal diets of animals, this level being adequate for growth of pigs fed milk-based diets.

Effects on reproduction have been documented in rats (Nielsen et al., 1975) and swine (Schnegg and Kirchgessner, 1975a; Anke et al., 1974), mainly in terms of increased mortality during the suckling period (rats) and smaller litter size (both species).

Nickel also appears to be essential for ruminants, the requirements of which are higher than for other animal species (Spears, 1984; Spears and Hatfield, 1977). Spears and Hatfield (1977) demonstrated disturbances in metabolic parameters in lambs maintained on a low-nickel diet (65 ppb), including reduced oxygen consumption in liver homogenate preparations, increased activity of alanine transaminase, decreased levels of serum proteins, and enhanced urinary nitrogen excretion. In a follow-up study, Spears et al. (1978) found that these animals had significantly lower microbial urease activity.

Schnegg and Kirchgessner (1976; 1975b) demonstrated that nickel deficiency in rats leads to reduced iron content in organs and iron deficiency anemia, resulting from markedly impaired iron absorption. Spears et al. (1984) found that additional nickel may also improve the iron and zinc status of neonatal pigs. The mechanism through which nickel might enhance iron absorption is still unclear. While nickel might act enzymatically to convert ferric to ferrous iron (a form more soluble for absorption), it might also promote the absorption of iron by enhancing its complexation to a molecule that can be absorbed (see below) (Nielsen, 1984).

Nickel also appears to adhere to other criteria for essentiality (Mertz, 1970), e.g., apparent homeostatic control, partial transport by specific nickel-carrier proteins (see Chapter 4), and specific requirements in a number of proteins and enzymes. Fishbein et al. (1976) have reported that jackbean urease is a natural nickel metalloenzyme. It is possible that rumen bacterial urease may also have a specific nickel requirement (Spears et al., 1977). In this connection, Mackay and Pateman (1980) found that a mutant strain of

Aspergillis nidulans, which is urease-deficient, requires nickel II for restoration of urease-activity. In particular, the strain carrying a mutation in the ure-D locus was responsive to nickel.

More recently, King et al. (1985) studied the activation of the calmodulin-dependent phosphoprotein phosphatase, calcineurin, by various divalent cations. Activation of calcineurin by nickel II was observed in the presence and absence of calmodulin despite the presence of high concentrations of chelators. Their study results suggested to the authors that nickel II may play a physiological role in the structural stability and full activation of the calcineurin enzyme.

To date, the most extensive evidence for identified, specific biochemical functions of nickel has come from studies of microbial systems. In such systems, the element is presented in: (1) the hydrogenases from several bacteria that mediate the Knall gas reaction ($2H_2 + O_2 \longrightarrow 2H_2O$) (Albrecht et al., 1982), (2) the sulfate-reducing bacterium Desulfovibrio gigas (Legall et al., 1982), and (3) the enzyme carbon monoxide dehydrogenase in acetogenic bacteria (Drake, 1982). Furthermore, a number of studies have established that nickel is the core metal in the tetrapyrrole, Factor F_{430} (see reviews of Thauer, 1982 and Nielsen, 1984), the cofactor for methanogenic bacteria enzymes mediating methane formation.

Evidence for the role of nickel in human physiology is not conclusively established. The study of Rubányi and co-workers (1982) showing profound, transitory increases in circulatory nickel shortly after parturition has been linked to a possible role in control of atonic bleeding and placental separation (see Chapter 4). In a recent review of trace elements, Nielsen (1984) postulated that nickel was likely required by humans and suggested that a dietary requirement of 35 μg daily (based upon extrapolation from animal data) could be reasonably expected.

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